A Treatise on Diphtheria.

By Dr. H. Bourges.

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A TREATISE

ON

DIPHTHERIA.

BY

DR. H. BOURGES.

TRANSLATED BY E. P. HURD, M.D.,

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1894.
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TRANSLATOR'S PREFACE.

Probably no disease is the subject of more general interest to physicians than diphtheria, as none is a more favorite topic of discussion at medical meetings. Recent bacteriological researches have wonderfully advanced our knowledge of its etiology, while the therapeutics of diphtheria have hardly kept pace with this progress. The remedies proposed are legion, but all too poorly fulfill their end, and the mortality from this disease still remains very high. We are still without a specific, though the profession is looking for one; but physicians are learning more intelligently to combat diphtheria, and the gains which prophylaxis has made are great.

Under the head of the nature of diphtheria, there are two points to consider: *first*, the question of its microbial origin; *second*, whether it is primarily a local or a general disease.

1. Till within a few years, nothing definite has been known about the contagion of diphtheria. There is now a growing disposition to accept as substantiated the claims alleged in behalf of the Klebs-Loeffler bacillus, especially in view of the recent confirmation of these claims by Roux and Yersin, of Paris, also by Drs. Abbot and Welch, of Baltimore. This bacillus is about as long and twice as thick as the tubercle bacillus; its extremities are rounded; it is immovable; it forms groups of chains, each element of which becomes club-shaped at its extremity. It is found exclusively in cases of diphtheria, in or beneath the false membranes; has been in vain sought in the blood and viscera. Culture experiments, made first by Loeffler in 1884, subsequently by Roux and Yersin, appear to

have been successful; and with the product of pure cultures, the disease in all its essential features—not even the secondary paralysis in the experiments of the French bacteriologists being lacking—has been reproduced in animals. These experiments have been in part confirmed by Kolisko and Paltauf, of Russia, and by Drs. Welch and Abbot, of the Johns Hopkins Hospital; the latter have noted the invariable concomitance of the Klebs bacillus with the false membranes of true diphtheria. Other associated microbes, which doubtless have a rôle in the necrotic phenomena, have been observed in diphtheritic membranes, notably the *Streptococcus diphtheriæ* of Prudden, which seems to be identical with the *Streptococcus erysipelatodes* and the *Streptococcus pyogenes*. Prudden, in fact, assigns to this micro-organism the principal part in the production of false membranes.

2. With regard to the second question, while there is not yet unanimity among the authorities, there seems to be *preponderant evidence* that diphtheria is primarily a local disease, the microbe first causing a local inflammation, necrosis, and fibrinous exudation, then elaborating in the false membranes a peculiar poison—a toxalbumen,—which is absorbed, infects and prostrates the organism.

It is true that there are difficulties attending this view in its application to all clinical cases; the gravity of the phenomena of infection is not always in proportion to the extent of the false membranes, and with an inconsiderable amount of local lesion the patient may from the first be overwhelmed by the toxic accidents. Cadet de Gassicourt makes much of this argument, and classes such cases under the head of "diphtheria of hypertoxic form." On the other hand, it is equally true that there are benign cases where,

with well defined patches of false membrane covering considerable areas, the constitutional symptoms are trifling and almost *nil.*

There seems to be no better way to arrive at a true conception of diphtheria than by pathological experimentation, the results of which always bear out the view above stated *of a primarily local origin of the disease.* This is not the place for a statement of facts such as Oertel has given in his article on "Diphtheria" in the first volume of Ziemssen's Cyclopædia, and which show conclusively that diphtheria, when induced in animals by the inoculation of bits of false membrane, is always at first local, fixing itself at the point of infection, *and thence radiating inwardly.* In harmony with this induction is the experience of Roux and Yersin with the soluble filtrates of diphtheritic cultures, which, injected in animals, produce septic accidents identical with the general constitutional effects of diphtheria in man. In accord with this doctrine, we may explain the grave hypertoxic cases as cases of unusual susceptibility to the disease, where the poison, though coming from only a small centre, is rapidly absorbed, and meets with but feeble resistance. In the *benign* cases alluded to, though the diphtheritic focus was of considerable extent, either the conditions for the elaboration and absorption of the poison were unfavorable, or the vital forces of the organism were peculiarly resistant to its influence; we are not without analogies which will enable us to understand such cases in conformity with the view that diphtheria is primarily a local disease.

The treatment of diphtheria will naturally vary somewhat in accordance with views held as to its being primarily a local or a general disease. Those who believe in a primarily local origin will naturally have

a strong interest in destroying *in situ* the morbid germs before they have had time to generate their virus and poison the organism. Under the other theory, the indications to promote local antisepsis and limit the spread of false membranes is equally recognized; but he who regards the diphtheritic *plaques* as only the expression of a general disease, bearing the relationship to the latter which the scarlatinal angina bears to scarlet fever, will not so strongly insist on energetic local treatment as he who looks upon the local lesion as the centre of the infection. Those, doubtless, that hold to the latter view have the most sanguine expectation that a specific will yet be discovered which, applied in time to the morbid focus, will nip the disease in the bud.

Certainly the results of the cauterization treatment, carried out with the intent of destroying the microbe *in situ*, have not been remarkably successful, unless we except the apparently favorable experience with carbolic acid and with phenicated camphor of Archambault and Gaucher, at the Hôpital des Enfants Malades; of Soulez, of Romorantin; of Sevestre, at Hôpital Trousseau; and of Dubousquet-Laborderie (*vide Bulletins et Memoires de la Société de Médecine Pratique*, January 15, 1889). The method of these writers has been so highly vaunted that it deserves mention. The phenicated camphor is made of follows (formula given by Sevestre):*

℞ Camphor, 20 parts.
Castor oil, 15 parts.
Alcohol, 10 parts.
Crystallized phenic acid, 5 parts.
Tartaric acid, 1 part.

Dissolve the phenic acid in the alcohol, add the camphor, then the tartaric acid, and finally the oil.

* Sevestre: "Études de Clinique Infantile," 1890, p. 210.

Gaucher applies this preparation in the following way:

"The mouth being widely opened and the tongue depressed, the operator will carry the swab charged with the liquid into the back part of the throat, applying it to the tonsils or other parts that are covered with false membrane. He will rub vigorously the diseased surface, in order to detach and remove the diphtheritic membrane, which will come away in débris or flakes. After each rubbing, the swab should be washed in a carbolic solution. These frictions should be repeated several times at each séance till all the white patches have been removed or destroyed. A final application with the swab dipped in the caustic will be made to the throat, in order to touch all the surfaces which have been denuded and despoiled."†

This operation is repeated morning and evening and in the interval of the cauterizations; large irrigation-injections are made every two hours into the throat, by means of a fountain syringe, of a 1:100 carbolic solution. The pain of the cauterizations is sometimes very great, but may be mitigated by previously spraying the throat with a cocaine solution.

Despite the fact that signal and unparalleled success is claimed for this treatment (see statistics of Gaucher, Le Gendre, Dubousquet), it will not be likely to come into favor, on account of the painfulness of the cauterizations, the swelling which follows them (which necessarily hinders deglutition), and the difficulty, if not impossibility, of application in young children. Theoretically, this method is excellent; practically it demands for its execution a pitiless

† *Bull. et Mém. de la Soc. de Méd. Pratique*, January 15, 1889.

hardihood which few physicians possess. It is doubtful if in private practice the results would ever be even approximately as good as the French writers claim. The method of cauterizations is an old method, dating back to the times of Bonsergent, who cauterized the throats of young children with a red-hot iron, and Bretonneau, who did not even originate but who borrowed from physicians of a past age a practice which consisted in swabbing out the diphtheritic throat three or four times a day with fuming hydrochloric acid. Trousseau, Rilliet and Barthez, and others adopted substantially this procedure, using muriatic acid, saturated solutions of nitrate of silver, sulphate of copper, etc., forcibly removing false membranes where they could, and cauterizing the denuded surfaces.

It is needless to say that the method of cauterizations, as formerly advocated by this school, has been deservedly pronounced a failure, and is now a thing of the past. Cauterization, as Cadet de Gassicourt says, does not prevent the patches from forming anew; it causes pain and dysphagia, and the more the derm is denuded the more the extension of false membranes is increased and promoted.

It may, however, be said, in defense of the later method proposed by Gaucher and his colleagues, that it is less severe than the methods of Bretonneau and his school, as phenic acid is comparatively a mild caustic, and, in the diluted form in which it is used, effects little destruction of tissue, while being nocuous or destructive to the microbes. It may well be, as these writers claim, that, in cases of adults where this heroic treatment can be properly carried out, it may save life where other methods fail, due pains being taken to keep the throat well disinfected in the inter-

vals of cauterizations by means of antiseptic sprays and irrigations. Most authorities condemn all interference with the false membranes till they are separated from their attachments, and can be removed without violence to the parts beneath them.

II.

At the meeting of the Société de Médecine Pratique, January 3, 1889, when the paper of Dubousquet was read, commending the method of cauterizations advocated by Gaucher, Guelpa (who made considerable stir in the Society discussions of diphtheria) demanded if the good results which had been claimed for this method might not have been due largely, if not altogether, *to the frequent irrigations* which formed a part of the treatment. The majority present at this and subsequent meetings were understood to deprecate all use of strong caustics, as well as the forcible removal of the false membranes.

At another meeting, held April 4th, and at a subsequent meeting of the Therapeutical Society, Guelpa read a long paper in answer to the question, "*Why, in the treatment of diphtheria, do the same medicaments give satisfactory results to some practitioners and negative results to others?*"

He criticised the numerous remedies which have been advised in this disease. Some, as resorcin, have been extolled as almost specific. This medicament, so successful in the hands of Callias, saving nearly all his patients, has not proved efficacious in the practice of Cadet de Gassicourt, who has used it in all degrees of saturation.

Phenic acid has been highly commended by

excellent authorities, notably Kempster, Jacobi, Oertel, Billington, Smith, and Mackenzie, but others have not found its effects especially favorable. The same judgment may be passed upon caustic soda and glycerin, lime-water, lemon-juice, boric acid, tannin, iodoform, and even perchloride of iron.

While recognizing the fact that there is a difference in the malignancy of epidemics, and that remedies act differently at different periods of the same epidemic, the writer, nevertheless, felt compelled to conclude that the same medicament in the hands of certain practitioners had given favorable results, while it had failed completely with others. The cause, he believed, he had found. We quote his words:

"M. Callias, repeating the trials with resorcin made by Andeer, Leblond, and Joja, is careful to tell us that he mops out the throat every hour, night and day, with a 5-per-cent. solution. To this he adds spraying the buccal and nasal cavities with a 2-per-cent. solution every two or three hours, and fumigations, twice or three times a day, with resorcin in substance, sublimated by a moderate heat. . . . . Note the fact that the throat is swabbed out *every hour night and day.* . . . . With regard to phenic acid, M. Roulin tells us that he employs his carbolic irrigations every hour in the twenty-four, and claims extraordinary success. Kempster and Rothe paint the throat every hour with a strong carbolic mixture, and use every half-hour a weaker preparation for a gargle. Giovanni Calligari applies every quarter of an hour to the diseased places a 1-per-cent. carbolic solution. Jacobi sprays and irrigates very frequently with carbolic solutions. Oertel declares that phenic acid constitutes the best and surest means at our dis-

posal for combating diphtheria. But this medicament should be employed with energy. The practitioner should spray every two hours, every hour, or oftener, according to the age of the patient, with a 5-per-cent. solution. The atomizing tube should be made to enter the patient's mouth. All practitioners have obtained excellent results from this frequent use of the carbolic preparations. Oertel, in fifty-one cases, did not lose a patient.

"If we come to the employment of perchloride of iron in diphtheria, we have still less difficulty in establishing the fact that the disease is the more surely and rapidly overcome the more frequently and thoroughly the part which is the seat of the disease is medicated with the solution employed. Thus, we see the Aubruns, father and son, administer to their diphtheritic patients a spoonful of a 4-per-cent. solution every five minutes during the day, and every quarter of an hour at night. Jacobi advises to give the solution of perchloride of iron every quarter of an hour, or every hour, according to the gravity of the disease. Colson, Clar, Noury also administered this medicament *about every half-hour, day and night.*"

It will be seen from the above extract that, in the estimation of the writer, it is the *frequency and thoroughness* with which the applications are made that are the principal elements of success. Firmly believing in the local origin of diphtheria, and that if the seat of the disease can be kept antiseptically clean the microbes will be impeded or thwarted in their development, and blood-poisoning and further extension by contiguity of the disease prevented, he advocates irrigations *every hour* of the nasal cavities (in the event of nasal diphtheria existing) and of the throat with a 5-per-cent. chloride-of-iron solution. For this

purpose, a common hand rubber-ball syringe will answer the purpose; the capacity of the rubber ball should be about four ounces. The nozzle, which should be of hard rubber, is inserted successively into each nostril, and the solution injected with sufficient force to penetrate the pharynx. When the irrigation is to be made by mouth, the nozzle can be inserted behind the last molar tooth. Generally there is no great difficulty. The child is held in the lap of the nurse or medical attendant, with the head pressed against the chest of the latter; and the cannula of the syringe is slipped in behind the last molar. Generally at this moment the mouth is opened wide in the struggle, and it is very easy to inject with full stream quite a quantity of the liquid. Part of the liquid is swallowed, but the most of it flows back. For the nasal douches a weaker solution is recommended (3 per 1000).

Guelpa regards these irrigations as of great use "in fortifying the surrounding mucous membrane and in washing away the septic products, whose absorption constitutes the true danger of the disease, and whose accumulation serves to irritate the contiguous mucosa and render it a fit soil for the development of the diphtheritic bacillus." As for parasiticides, there are probably at least a dozen agents, any one of which, if used with sufficient frequency, will almost equally well fulfill the leading indication; phenic acid and perchloride of iron are among the safest; resorcin demands further trials; corrosive sublimate (1 to 5000) would probably be the best if the free use of this bactericide were not attended with some danger. The intent of the irrigations is not to clear the throat or other diseased surface of false membranes; the false membrane, says Guelpa, need give no trouble as long

as it remains *within certain fixed limits*. The true end of treatment is to prevent the pseudo-membrane spreading over too large a surface. If the false membrane is not allowed to extend, if the subjacent tissues are not irritated by the treatment, the diphtheritic patches will become loosened, and fall off in the course of a week; if other patches form in their places, these are always more limited, are thinner, and sooner mature and fall off.

Cousot, of Brussels, in the *Journal de Médecine et de Chirurgie Pratique*, April, 1889, also insists that the treatment of diphtheria at its commencement should be chiefly local; that it should destroy the germs of diphtheria wherever they appear; should entirely prevent putrefaction, and, at a later stage, when systemic infection occurs, local remedies should still be vigorously applied, and additional measures employed to relieve the general symptoms. The medicine for local use which Cousot believes best fulfills these indications is a mixture of acacia, spirits of peppermint, and tannin, employed in the following formula:

Mucilage of acacia, 100 parts.
Tannin, 10 parts.
Spirits of peppermint, 2 to 20 parts.

The syringe is employed for its application, for this alone permits sufficient irrigation and impregnation of the inflamed surfaces. If the false membrane occupies the pharynx, tonsils, or nasal fossæ, whatever may be the degree of its development, it is necessary to inject the mucilage and tannin into the mouth and nares *every two hours*. Whatever may be the degree of decomposition of the diphtheritic patch, its putrid odor ceases on the first application, and it contracts and becomes detached. The efficacy of

this method seems to be established by abundant statistics.*

Whatever may be said of the efficacy of irrigations, they are not always easily administered, and the pursuance of this treatment every hour or two day and night is certainly fatiguing to the patient, and must more or less interfere with sleep. To be sure, according to the French authorities most zealous in advocating these injections, in a disease fraught with so much danger as diphtheria, that treatment which will save the most lives should be adopted, no matter how difficult of execution. The question, then, for solution is this: Is the method of frequent irrigation the best method of meeting the indication? Good authorities have claimed most excellent results from milder measures. Thus a child may be made to frequently swallow a solution of chloride of iron without great difficulty, and this would appear to accomplish the same end as the forcible injection of the same fluid. Sprays containing carbolic acid can be used alternately with the mixture, and port wine (which contains tannin and alcohol) can be administered freely in the interval. An occasional irrigation, or even mopping out the throat, may be practiced, the swabbing being done with due gentleness, so as not to cause lesions or excoriations, to be new centres of infection.

These are the principles of treatment advocated by numerous American authorities, as J. Lewis Smith, Abram Jacobi, C. E. Billington. Smith and Billington make much account of the frequent administration of tincture of chloride of iron. The following is a favorite prescription of the latter:

---

* Cited from Sajous's "Annual."

℞ Tinct. ferri chloridi, ʒ iss.
Glycerin, }
Water, } ää f ℥ j.

M. Sig.: A teaspoonful every hour.

Smith gives about the same quantity of iron hourly, combined with four grains of potassium chlorate; the vehicle is simple syrup. Both deprecate forcible removal of the pseudo-membranes and all energetic topical applications by sponge or probang. Besides the hourly dose of chloride of iron, Billington gives every hour a teaspoonful of a mixture of lime-water and glycerin, in which a little chlorate of potassium is dissolved. Both make much account of spraying with the hand atomizer, and prescribe solutions of carbolic acid and lime-water for that purpose. A favorite combination of Billington's is the following:

℞ Acid. carbolic., ♏xv.
Aquæ calcis, f ℥ vj.

M. Sig: To be applied to the throat very frequently in the form of spray.

In nasal diphtheria, the nares should be syringed out two or three times a day with salt and water, then with a mixture of salicylic acid, ten grains, with thirty of sulphate of sodium, to glycerin half a fluidounce, and water two and a half fluidounces. For this injection, a hard rubber ear-syringe may be employed.

In adult patients, with particularly unyielding diphtheritic patches, once or twice a day a mixture of tincture of chloride of iron two parts, glycerin one part, may be carefully applied to the surface of the membrane with the tip of a camel-hair pencil. It seems, says Billington, to shrivel up the membrane and hasten its disintegration. But strong applications should

never be "mopped" over the inflamed throat, and it is not thought safe, as a rule, ever to apply a brush to a child's throat.

III.

Fresh evidence has been steadily accumulating to prove the invariable causal connection between Loeffler's bacillus and ordinary diphtheria, and Prudden has recently made an important communication in which he concedes to this microbe the primary rôle in the etiology of this disease (*Medical Record*, No. 1067). Dr. Welch, of the Johns Hopkins University, has published the results of his and Dr. Abbot's studies at the Johns Hopkins Hospital, and these add striking confirmation to the data on which has been founded the doctrine of the primarily local origin and development of the infection—a doctrine which, we observe, has been lately conceded by Cadet de Gassicourt, though opposed in the first edition of his masterly work, "Leçons Cliniques sur les Maladies des Enfants" (t. iii, 1884).

"Of capital importance," says Professor Welch, "is the establishment of the fact that the diphtheritic bacillus develops only locally at the site of infection, and does not invade the tissues or the circulation. It is found only in the diphtheritic pseudo-membrane, and not even in the subjacent mucous membrane. Indeed, it is only the superficial parts of the false membranes which contain the bacilli. The determination of this fact gives at once a clear and decisive answer to the long-mooted question as to the primarily local or constitutional nature of diphtheria. The germ which causes this disease not only makes its first appearance and multiplies where the pseudo-

membrane is formed, but it does not even subsequently invade the blood and organs. As we shall see later, the constitutional symptoms are due to the reception of a chemical substance or substances of remarkable toxic properties produced by the local development of the diphtheritic bacillus."*

We are, then, again brought around to the primary indication of treatment, made more and more certain and imperative as researches accumulate: *to destroy the contagium in situ before the microbes have had time to elaborate their poisons and infect the organism.*

It would seem that diphtheria primarily occurring on any accessible *cutaneous* surface might always be readily arrested by deep, thorough cauterization. Such cases are, however, very rare, and, when they occur, generally follow inoculation of a wound. The primary lesion is too often on mucous surfaces, which, like the posterior nares and the larynx, are not easily amenable to thorough topical treatment.

What shall be the treatment of the toxæmia resulting from absorption of the poisonous principles produced by the bacilli? Every physician is familiar with the change which often takes place at a variable time—two, three, or four days—after the first appearance of the patches; the sthenic symptoms, on which hope was based, give way to symptoms of prostration, and the system seems overwhelmed by a paralyzing poison.

Ignorant of the proper antidotes of this poison, if such exist, we can only combat it on general principles, by stimulants and tonics. The internal employment of corrosive sublimate in frequent doses of $\frac{1}{100}$ to $\frac{1}{4}$ grain, or of calomel ($\frac{1}{6}$ to 1 grain every hour), is no longer justified on the ground of a microbicidal

**Medical News*, May 16, 1891, p. 559.

action exercised by these drugs, for the constitutional symptoms are not due to microbes, but to their soluble products, and there is no evidence that mercurials destroy these products in the blood.

The same judgment must be passed upon the sulphites and hyposulphites, counseled by Giacchi and Polli, in Italy, phenic and salicylic acids, vaunted by Besnier in France and Foutheim in Germany, and benzoate of sodium, recommended by Helferich, Sanné, Love, and others.

If the internal use of corrosive sublimate has been attended with good results, these might very properly be attributed to the topical action of the mercurial while passing over the mucous membranes in the act of deglutition, and not to any effect on the blood. *Per contra*, there is reason to believe that the *tinctura ferri chloridi*, one of the best topical remedies, may exercise beneficial constitutional effects. Recent investigations (as those of Ferguson) have shown that the diphtheritic poison rapidly spoils the blood-corpuscles; there are still lacking observations which directly show that tincture of iron retards this disintegration, although good authorities, basing themselves on large clinical experience, believe that this preparation, freely and continually administered, does have this power. Dr. Whittier believes that this medicine, given so as to saturate the system, is the best that can be employed. Baruch prescribes hourly doses, in quantity varying from eight to twenty-five drops, mixed with glycerin and water. Food and stimulants are administered before the iron, but not immediately afterwards, so that the iron may first have a local effect on the fauces.

"That now, after thirty years' constant use of the tincture of chloride of iron in both hemispheres,

there is an almost unanimous verdict in its favor, renders it probable that the few who have not observed good effects have treated unusually bad cases, or have given the medicine in small and inadequate doses." (Dr. J. Lewis Smith.)

The employment of pilocarpine (either by potion or by subcutaneous injection), first recommended by Guttman, has gone out of use. Archambault, Schmidt, Alfoldi, Jacobi, and J. Lewis Smith have pointed out the dangers of this treatment. Sudden filling up of the bronchial tubes with secretion, and heart-failure, have not unfrequently followed its use.

Quinine has been much prescribed in diphtheria, and when given in sufficient doses doubtless does have some tonic effect; it is, however, depressing in large doses, and, on account of its bitterness, is always repugnant to children. "It does not," says Smith, "seem to exert any decided action upon the local affections or blood-poisoning in diphtheria."

The same judgment may be passed on the internal administration of chlorate of potassium, a remedy, doubtless, too much administered, being of no specific value, and being toxic in large doses.

Alcoholic stimulants have an important place in the therapy of diphtheria, and many authorities, as Jacobi, recommend quantities that in health would be toxic. J. Lewis Smith does not hesitate to give a teaspoonful of good brandy or whiskey hourly to a child of five years, and Jacobi states that he has often seen children get well with ten ounces a day who were doing badly with three or four. Cadet de Gassicourt ("Traité Clinique," etc., t. iii) would give to a young infant from half an ounce to two ounces of old rum or brandy per day.

Caffeine, camphor, strychnine, and Siberian musk

have been recommended to counteract depression and heart-failure. Jacobi believes musk to be the best stimulant in urgent cases of heart-failure. "If," he says, "ten to fifteen grains, given [in thin mucilage] within three or four hours to a child of one or two years, do not restore a healthy heart action, the prognosis is bad."

Zannelis (*Bull. et Mém. de la Soc. de Méd. Pratique*, 1889) speaks favorably of strong infusions of tea or coffee in adynamic stages. Nourishment should be for the most part liquid, for obvious reasons; the digestive functions are depressed, and the frequent ingestion of medicine and alcoholic stimulants more or less interferes with the secretion of gastric juice and the formation of peptones; the mechanical obstacles to deglutition are frequently considerable, and anorexia is generally a marked symptom in the toxic stage. Hence milk, beef-juice, liquid peptones, raw eggs beaten up in milk, given in such quantities as can be tolerated and *not too often* to interfere with the administration of antiseptic medicines and of alcoholic stimulants, are especially ind cated.

In concluding this rather long therapeutic *résumé*, I would repeat that physicians are likely to profit more and more from the exact knowledge which we are acquiring of the nature of diphtheria. All *pathies* must sink into insignificance before scientific medicine, and the Bacterial Pathology is giving us a scientific basis for therapeutics.

The importance of the new etiology has justified a restatement of the whole subject, and therefore the present treatise by a well known French pathologist and master of bacteriology will be welcome in an American dress.

E. P. HURD, M.D.

Newburyport, Mass., Jan. 1st, 1894.

AUTHOR'S PREFACE.

Diphtheria is a contagious disease due to the bacillus discovered by Klebs and studied by Loeffler. The point of infection chosen by this bacillus is almost always a mucous surface, the pharynx or the air-passages preferably (sometimes an excoriated region of the cutaneous surface); here it forms colonies and pullulates, determining the development of a fibrinous pseudo-membrane, of which it occupies the superficial stratum. There the microbe remains entrenched, never invading the organism nor entering the circulation. It may, in the same subject, be transplanted to many different points of the mucous or cutaneous surface, but causes only foci of local infection. But though the organism does not become infected in its entirety, it may be poisoned, for the bacillus produces a very active toxine, demonstrated by Roux and Yersin, which is readily diffusible and penetrates the circulation.

This disease comprehends two orders of symptoms: the one (localized at the point of infection, and harmful only by the mechanical accidents which it may provoke, such as the obstruction of the air-passages by the false membrane) due to the bacillus; the other, marking a profound poisoning of the organism by the diphtheritic toxine, manifests itself by grave general troubles and profound lesions of the viscera. Diphtheria, then, is the resultant of these two agents, the bacillus and the poison.

We are thus led in the description of the disease to class under two distinct heads the symptoms and lesions, according as they are due to the bacillus or to the diphtheritic poison. Often, too, in the course of diphtheria, a new microbic infection grafts itself upon the first; hence a third division, that of Secondary Infections.

Such is the plan of our study of diphtheria. To the objection that the lesions and symptoms of the diphtheritic poison and of the secondary infections, respectively, have not yet been sufficiently studied or differentiated to insure accuracy in classification, it may be answered that further researches will bring about the necessary rectifications; meantime the general plan which I have adopted seems to agree best with what is now known of the disease.

I have given very extensive proportions to the chapter on Bacteriology, and endeavored to furnish a description sufficiently minute and practical to enable those who have only elementary notions of bacteriological technics to repeat the principal experiments. Moreover, the cultivation of the diphtheritic bacillus will ultimately constitute a capital and indispensable element in the diagnosis of the disease. I have devoted a special paragraph to the false diphtherias, although the study of these, only recently undertaken, is far from being complete; this inchoate and undeveloped condition stimulates to further tentatives in this direction.

Lastly, I have not filled my book with the innumerable variety of therapeutic methods and agents which have been proposed for diphtheria; their very abundance gives the measure of their value.

A TREATISE ON DIPHTHERIA.

HISTORY.

Several names deserve to be inscribed at the head of the history of diphtheria: that of Bretonneau, who made of this disease a morbid entity and gave it its name; that of Klebs, of Loeffler, who discovered the bacillus of diphtheria and determined its specificity; those of Roux and Yersin, who separated the poison of the bacillus and demonstrated its action.

The history of diphtheria really commences with Bretonneau. It is true that divers manifestations of the disease had been recognized and often well described from the most remote antiquity. Such was the case with the Syriac or Egyptian ulcer observed by Aretæus, of Cappadocia, and after him by Galen and Cœlius Aurelianus. We must then come down to the sixteenth century to find descriptions referable to diphtheria. An account of an epidemic of angina in Holland was written by Pierre Forest in 1557, and mention of pestilential anginas observed in Germany in 1565 is made by Jean Wierus. From this time onward, the disease is more frequently described, in

the seventeenth century under divers names; *garotillo* in Spain, *angina ulcerosa* in Portugal, *morbus strangulatorius* in Italy. Next come the epidemics, better studied, of the first half of the eighteenth century: that of Paris (gangrenous sore throat of Malonin and Chomel the elder); those of England, described by Fothergill, Starr, and Huxham; those of Sweden and of Germany.

But up to this time the manifestations of diphtheria were regarded as expressions of gangrene: the false membrane was an eschar, and each localization of the disease was considered as a distinct affection.

Home, in 1765, studied especially the laryngeal manifestations of diphtheria, and described them as a new disease under the name of croup. He was the first to recognize that the false membrane is not the product of gangrene, but of a superficial exudation. But he did not see the link which unites croup to malignant angina, and he regarded them as two distinct diseases. In 1771, Samuel Bard essayed to demonstrate that simple angina, angina with extension to the larynx, and laryngitis when occurring alone, are but forms of the same disease. He considered the false membrane, not as an eschar, but as formed of concrete mucus. He could not, however, modify the opinion generally entertained, and the profession still continued to regard croup as a special disease.

The question of croup being under discussion, and a prize having been offered by Napoleon I., in

1807, for the best treatise on the subject; in one of the five memoirs that were regarded as especially meritorious—that of Jurine, of Geneva—we find emphasized the reservations already formulated by Bard and Horne respecting the gangrenous origin of malignant angina; and, moreover, Jurine affirms that croup is a frequent consequence of this kind of angina in children. These notions, however, remained undeveloped until Bretonneau published the results of his labors (1818–1826). He showed that the false membrane of the larynx and trachea is continuous with that of the throat and nasal fossæ, hence there is identity of nature between the different localizations of one and the same disease, to which he gave the name of *diphtheritis* (from *diphthera*, a membrane). He endeavored to prove that the false membrane is but a fibrinous exudation covering the intact mucosa, and he maintained, even, that the ulcerous and gangrenous processes cannot be coincident with diphtheria. In his estimation, the disease is characterized by a specific local inflammation.

Trousseau continued the researches of his master, but modified the conception of Bretonneau on the nature of the affection. He made of it a general infectious disease presenting the property of determining upon different points of the economy a pseudo-membranous inflammation. He considered the false membrane not as an initial phenomenon, but as a consequence of the infection, and proposed to replace

the word *diphtheritis*, which gives too much prominence to the factor of inflammation, by the name *diphtheria*, which better designates a general disease. These notions, now recognized as inexact, since the bacteriological labors of Klebs and of Loeffler have been confirmed, nevertheless led Trousseau to the correct conclusion that death from diphtheria may be independent of the asphyxia, and the consequence simply of the systemic poisoning. Trousseau's error in regarding diphtheria as a general infectious disease was repeated by almost all pathologists up to the last few years.

Despite Bretonneau's brilliant discoveries, the German school, under the leadership of Virchow, entrenched itself behind the anatomico-pathological findings, and again separated diphtheritic angina from croup. The microscope shows that below the false membrane in the pharynx the inflammation penetrates profoundly the chorion—is interstitial, in fact —while it remains quite superficial in the larynx and trachea. The German school admitted, then, two distinct diseases: one an infectious angina easily becoming gangrenous; the other, exudative and purely inflammatory—croup. Virchow and his pupils went still farther: the words *diphtheria* and *croup* served to designate lesions of quite different origin. Every interstitial inflammation of the tissues became in their eyes diphtheritic, every superficial fibrinous exudation croupous. Thus it came about that ulcero-mem-

branous stomatitis was ranked among the diphtheritic inflammations; and there was a croupous nephritis, and a croupous pneumonia. These notions, which soon began to lose the support of clinicians, were destined to be abandoned when bacteriology demonstrated their falseness.

After Bretonneau and Trousseau, the clinical features of diphtheria became well defined, and the pathological anatomy of the lesions was developed and elucidated by Virchow, Cornil, and others. At the same time the microscopy of the lesions was not advanced, and the intimate nature of the disease was unknown down to the time of the rise of microbiology and the development of modern views of infection. Some incomplete researches had been made in this direction when, in 1883, at the Congress of Wiesbaden, Klebs declared that he had stained a bacillus found in the false membranes of diphtheritic patients, which he considered as the specific agent of the disease. According to his investigations, the bacilli of diphtheria scarcely attain the dimensions of those of tuberculosis; they begin by grouping themselves in the epithelium of the mucosa, whereupon an enormous dilatation of the vessels below the epithelium occurs, with blood stasis. Then follows the exudation of fibrin which raises the epithelium filled with bacilli. Klebs declares he has not been able to note the presence of these micro-organisms in the viscera, although there were lesions in the lungs, the kidneys, the myo-

cardium, and the peripheral nerves; gentian violet and methylene blue, which stain the parasites in the false membrane, do not show their presence in sections of the viscera. He put forth the hypothesis that the lesions of the viscera may be produced by an irritant chemical substance furnished by the bacilli which pullulate on the surface of the diseased mucosa.

The year following, Loeffler published in a long memoir the results of his brilliant labors on the bacillus of Klebs. He was the first to isolate and cultivate it. Blood-serum is, he says, a good culture-medium. In a series of twenty-five cases of diphtheria, he almost always noted the bacillus in the false membrane, but never in the organs. With pure cultures he was able to provoke the formation, on excoriated mucous surfaces, of false membranes identical with those of diphtheria in the pigeon, the hen, the hare, and the guinea-pig. He has studied the effects of subcutaneous or intra-venous inoculation of the bacillus in a great number of animal species. Certain reasons leave him hesitating as to the specificity of this microbe. In several cases of typical diphtheria he was not able to discover it, and the animals inoculated never presented true paralysis. Lastly, in one case he found a bacillus identical with that of Klebs in the saliva of a healthy child.

In 1887, in a second memoir, Loeffler announced that in ten new examinations of diphtheritic mem-

branes he had found Klebs's bacillus in all. He also noted in the false membranes the pseudo-diphtheritic bacillus, much resembling the first, but without virulence when inoculated in animals.

The preceding year, 1886, D. Espine reported to the Swiss-Romande Medical Society that he had noted the presence of the bacillus in preparations made with false membranes, and its absence from the non-diphtheritic anginas with white exudations. In 1887 he confirmed his first discoveries.

At the end of the year 1888, Roux and Yersin began the publication of a series of memoirs on the diphtheritic bacillus. They established the existence in animals of experimental paralyses consecutive to the inoculation of Loeffler's bacillus, and thus overthrew a strong argument of the opponents of the specificity of this bacillus. They also confirmed the constant presence of this agent in the false-diphtheritic membranes, studied its resistance, the attenuation and the reawakening of its virulence, and made new researches on the pseudo-diphtheritic bacillus of Loeffler and Hoffman, which they identified with the specific bacillus of diphtheria.

But the most brilliant result of their labors was to show that the bacillus of Loeffler produces a poison of extreme activity—that the culture-broths, freed from microbes by filtration through porcelain, and then inoculated in animals, determine symptoms and lesions identical with those produced by injections of the cultures of the bacillus itself.

Since then, recent researches have shown that by the side of the pseudo-membranous products due to Loeffler's bacillus, there exist false diphtherias provoked by different microbes.

During the last few years, attempts at vaccination of diphtheria in animals have been made by Fraenkel and by Brieger and Behring. The results obtained by the latter seem very encouraging.

Before concluding this chapter I may refer to the researches on the diphtheritic bacillus by Darier, Babes, Soerenson, Kolesko, Paltauf, Zarnicko, Ortmann, Spronck of Utrecht, Escherich, and Klein; on the diphtheritic poison, by Brieger and Fraenkel, Wassermann and Proskauer, and Gamaleïa; on the secondary infections in diphtheria, by Darier, Prudden and Northrup, Mosny, Morel, and Netter.

ETIOLOGY AND BACTERIOLOGY.

General Etiology.—It is to-day undisputed that the efficient cause of diphtheria is the Klebs, Loeffler bacillus.

We have no certain notion as to the geographical origin of diphtheria, and may say with Trousseau that it is met at all seasons and under all climates. While formerly known mostly as as epidemic disease, it is to-day endemic in most of the great cities, and prevails much oftener than formerly in the country. Diphtheria generally appears in an epidemic form. In a country where this disease has seldom or never before been known, it first attacks a few isolated subjects, then spreads, multiplies its victims, and finally becomes extinct, only to reappear later. Generally the contagion has been brought by a patient or by infected objects from some locality where the disease had been prevailing. In other cases, there is a sort of reawakening of germs left in the locality by a previous epidemic—germs which had long remained inoffensive.

Whether the disease be epidemic or endemic, it is transmitted by contagion. Just here a nice question arises: Is contagion indispensable to the development of the disease? In other words, may a healthy subject be attacked by diphtheria without taking the specific germ from a person afflicted with the disease? We cannot at present give a positive answer to this

question. In studying, farther on, the pseudo-diphtheritic bacillus of Loeffler, we shall see that there exists a bacterium which, not yet differentiated morphologically from the bacillus of diphtheria, is distinguished only by the absence of virulence. Now this bacterium is found very frequently in the saliva of healthy persons, and some have been disposed to identify it with the Klebs-Loeffler bacillus, which may also remain inoffensive in the organism until quickened into virulence by some unknown stimulus. We have here an hypothesis similar to that which tends to confound the *Bacterium coli communis*, a microbe constantly present in fæcal matters, with the bacillus of Eberth, the pathogenic agent of typhoid fever. If this notion should be established, our mode of conceiving of the origin and manner of development of infectious diseases would have to be materially modified in many points. While waiting for such proof we may limit ovrselves by noting that observation demonstrates the importance of contagion in most cases.

The contagion of diphtheria may be transmitted either directly or indirectly. The direct method of contagion is no longer disputable, whether it be brought about by immediate contact or by inoculation. Persons who have the care of a diphtheritic patient are often contaminated by the saliva or false membranes which the patient ejects; in this way the medical attendant or nurse may contract diphtheria.

But indirect transmission is much more frequent. Those who attend the patient (nurses, relatives, or physicians) are oftener the carriers of the contagion, which adheres to their fingers or their clothing. Physicians have even communicated it by unclean bistouries or tongue-depressors. Books and playthings, as well as articles of clothing, have carried the specific germ. Children have taken the disease by riding in a coach previously used to convey a diphtheritic patient home or to the hospital. Food, even, may contain the bacilli; milk has more than once been the vehicle of contagion. If the contagious element is not very diffusible, nevertheless dried particles of false membrane may be wafted in the dust, and, being inhaled at a distance, may thus impart the malady. In Zurich the streets are thoroughly swept on certain days (Wednesdays and Saturdays) and the dirt-carts remove the rubbish; on these days Klebs has noticed an unusual number of cases of diphtheria to take their start, following, as it were, in the wake of the sweepers.

Is diphtheria always of human origin? Do we not meet in certain animals, as pigeons, hens, cats, hares, and even cattle, pseudo-membranous affections which may communicate diphtheria to man? A number of writers admit this source of contagion, basing their opinion on the coincidence of certain epidemics of human diphtheria with pseudo-membranous affections of domestic animals. For a similar

reason some have affirmed the propagation of diphtheria by dung-heaps. It must, however, be admitted that all the bacteriological researches seem to demonstrate that these pseudo-membranous affections of fowls have for origin microbes different from the bacillus of Loeffler.

At what epoch of the disease is diphtheria contagious? Possibly before the appearance of false membranes; but it is so at the highest degree when the false membranes are present, and eminently so during convalescence when the diphtheritic products are cast off. We know too that the saliva, when the false membranes are gone, may still contain the bacillus with all its virulence. Naturally, at such times, the occasions for contagion are abundant, for the patient will have returned to his ordinary mode of life.

If the resistance of the diphtheritic bacillus is relatively feeble in the living organism, and if it cannot preserve its virulence longer than one or two months in a person convalescing from diphtheria, it has a longer vitality under other circumstances. The contagion may cling to objects of bedding, of furniture, etc., and keep all its virulence for years, as numerous examples prove. An instance in point is related by Sevestre. In a village of Normandy, in other respects healthy, a lad 14 years of age was attacked by diphtheria; and several days later a number of cases broke out in the village. In investigating the cause of this

epidemic, Dr. Legrand remarked that the houses in which successively appeared the cases of the disease were situated by the side of two roads which connected the several parts of the village; but he could not explain how the first case originated, for there had been no diphtheria in the region for twenty-three years. Several days before the outbreak, the grave-digger had dug up the ground in the parts of the cemetery where the children had been buried twenty-three years before, and had even handled the bones; in this work he had been assisted by his son, who was the first to be attacked with diphtheria about a week afterwards.

Diphtheria is a disease of childhood, met most frequently between the ages of two and five years; it is rare in the new-born and in adults; very exceptional in the aged. It is a disease of winter, of damp, chilly weather. Certain local predispositions favor its appearance. It is certain that persons affected with an acute or chronic inflammation of the throat, hypertrophy of the tonsils, ulcerous lesions of the nose, lips, mouth, are more likely than persons not so affected to contract diphtheria. A first attack gives no exemption or immunity against another. Among the conditions which put the organism in a state of receptivity, we may mention the eruptive fevers, puerperality, defective hygienic conditions, uncleanliness, poverty with its attendant miseries.

To cause diphtheria, the Loeffler bacillus must

come in contact with an excoriated mucous membrane or cutaneous surface, thus prepared for the inoculation; fixing itself there, it provokes the development of a false membrane, in which it lodges; there it lives and multiplies, remaining in the most superficial strata; it lives always outside of the organism, which it poisons by the toxine which it secretes. This is not all. If Loeffler's bacillus is necessarily present in the false membranes, there are other micro-organisms associated with it, some of which are pathogenic and may modify the course of the disease by producing secondary infections.

We must study the bacillus, the poison, and the secondary infections of diphtheria.

[The statement that the Klebs-Loeffler bacillus *never* penetrates the mucosa, *never* invades the glands, the internal organs, the blood, is contradicted by other authorities, notably Drs. Abbott and Ghriskey of the Johns Hopkins Hospital (*vide* the April, 1893, number of the *Johns Hopkins Bulletin*). In the same number of the *Bulletin*, Dr. Howard reports a case of ulcerative endocarditis due to the *Bacillus diphtheriæ*. Dr. Flexner also reports a case of diphtheria with broncho-pneumonia in which he found isolated diphtheritic bacilli in the broncho-pneumonic areas.—Translator.]

The Diphtheritic Bacillus.—The most ready, the most simple, though at the same time the most incomplete, way of studying the bacillus of Loeffler, is

to look for it in suitably stained microscopic preparations of the false membrane. Bits of the exudate may be rubbed over the slides and stained, or sections may be made of the membrane hardened in alcohol. If the patient be a child, keep the tongue out of the way by a tongue-depressor; if need be, wedge the mouth well open. With a long curved forceps, catch hold of and remove a bit of the exudate, or remove it by means of a suitable well-sterilized swab. The instruments, of course, must be thoroughly aseptic.

If the examination is not to be made immediately, place the bits of false membrane in a sterilized test-tube, which should be closed with a plug of antiseptic cotton. When you are ready to make the examination, scratch the surface of the false membrane with the point of a sterilized platinum wire, and smear several slides, which must then be dried, stained, and examined. If the exudation has been collected on a swab, rub the slides with it, and dry them by placing them on a sheet of blotting-paper, the surface containing the preparation being turned upward. When it is sufficiently dried, pass the slide three times through the flame of an alcohol-lamp, the same side upward. Lastly, dip the slide into the staining fluid. There is nothing better than the alkaline solution of methylene blue, called Loeffler's blue:

Saturated alcoholic solution of methylene blue, 30 Cc.
Distilled water, 100 Cc.
Caustic potash, 1 centigramme.

It is better to extemporize this solution for each examination, and to employ it only when fresh. Keep in one bottle a solution of potassa (1:10000), and in another bottle a saturated alcoholic solution of methylene blue. At the moment of the examination, fill a watch glass with the potassa solution and add a few drops of the methylene-blue solution, till the surface of the staining fluid is no longer translucent. The glass slides must be withdrawn at the end of a few minutes and washed under a stream of filtered water. The preparation may then be wiped with a piece of woolen cloth and mounted. If you wish to preserve the slide, mount in Canada balsam.

Gentian violet is a good staining fluid, or Roux's blue, of which the composition is as follows:

Aqueous solution (1 per cent.) of violet dahlia, 1 part.
Aqueous solution (1 per cent.) of methyl green, 3 parts.
Distilled water, enough to obtain a moderately blue tint.

This solution does not precipitate, and keeps clear. It suffices to put on your prepared slide, after it is dried, a drop of this blue, and let it stain thoroughly the object; wipe off the excess of coloring matter with blotting-paper, and it is ready for the microscope. Use an immersion lens, and you will see that among all the bacilli of the false membranes the diphtheritic bacilli stain the most quickly and the most intensely.

This bacillus presents itself under an aspect very much like Koch's, but it is twice as thick, the extremi-

ties are rounded, sometimes pear-shaped; some rods appear strangled in places, others granular, because they take the staining unequally. Many are curved. In many points they are grouped in little masses.

If in certain grave cases we meet these bacteria almost exclusively in the false membranes, generally they are mingled with a great quantity of different microbes, all well stained. These are the habitual microbes of the mouth: large filaments of leptothrix, large micrococci, staphylococci, and streptococci, bacilli larger and longer than the diphtheritic bacillus, and others shorter and more stunted. It is not always easy in the midst of these bacteria to distinguish the Loeffler bacillus, and it is very much to be regretted that we have not yet found for its detection a method as sure as those which enable us to detect the bacillus of tuberculosis.

When a false membrane has been placed in absolute alcohol, it becomes hardened at the end of a couple of days. Then we can make sections and stain with Loeffler's blue or by the method of Gram. We note, then, under the microscope the situation of the micro-organisms in the false membrane. In the most superficial layer, the farthest from the mucosa, are seen in great quantity numerous quite varied microbes. Immediately below, but still quite far from the deeper portions of the false membrane, are the Loeffler bacilli, grouped in little characteristic masses in the fibrinous reticulum.

In order to isolate and cultivate the Loeffler bacillus, you should select, if possible, a case which is toxic from the onset, with thick false-membranes; and, with a platinum wire, scrape from the pseudo-membranous patches in the throat the débris which you wish to sow and cultivate. You can obtain good cultures with fresh pseudo-membranous débris, in an aseptic test-tube. If not prepared to begin the culture at once, dry the false membranes on filter-paper, for the dried bacilli are endowed with great resistance. Then, when you are ready to sow the material, let the false membrane soak a short time in a little filtered water; then scratch off a bit of the false membrane with the point of a sterilized platinum wire—the wire should be rather large and stiff, so that you can scratch off quite a piece. With this wire you may sow three or four test-tubes filled with the serum.

Serum is the best culture medium for the diphtheritic bacillus; it grows in all kinds of serum rapidly and abundantly. Loeffler gives the preference to this medium; his formula is as follows:

Serum of calf or of sheep, 3 parts.
Veal broth, neutralized, 1 part.
Peptone, 1 per 100.
Glucose, 1 per 100.
Sea-salt, ½ per 100.

But the blood-serum of horses or cows yields good results. By a daily exposure, of two hours' duration,

to a temperature of 58° C. in the dry-heat stove, repeated for five consecutive days, sterilization is effected; then an elevation of the temperature to 70° C. will accomplish gelatizination. Or the blood-serum of ascites or of pleurisy may be employed, though I have found this culture medium to give less satisfying results.

Place the tubes of serum in the dry stove at 37° C. Remove them at the end of eighteen hours. If the case be really one of diphtheria, the tubes will contain a great number of colonies, for in serum the Loeffler bacillus excels almost all other microbes in the rapidity of its multiplication. So that if the colonies are numerous, one may almost prejudge the nature of the disease, as tubes sown with exudates not diphtheritic present few colonies or none at all in the first twenty-four hours. The colonies of the Loeffler bacillus present the form of grayish-white spots, opaque in the centre, as large as the head of a pin. In the serum-tube first sown the colonies are not generally isolated, but by their grouping give the figure of a continuous streak; in other tubes, however, especially the last sown, it is very easy to study them separately.

There are a few other bacilli which form colonies in as short a time as the Loeffler bacillus. There is first a coccus that grows very well on serum; after twenty hours its colonies are very similar, as seen by the naked eye, to those of diphtheria, but after thirty-

six or forty-eight hours in the stove they are less voluminous than diphtheritic colonies of the same age, and take, moreover, in ageing, a very characteristic yellowish tint. Other cocci form in serum, after the first twenty-four hours, colonies whose aspect is identical with those of the Loeffler bacillus; their coloration is not modified with time, but their development is slower than that of the microbe of diphtheria. Lastly, you will sometimes find a very large coccus which liquefies the serum.

It is very evident that diagnosis cannot be safely established by a naked-eye examination of cultures; use a platinum wire to convey a minute portion of the suspected colony to the microscope for verification.

To obtain a pure culture, charge the platinum wire with a new portion of the verified colony, and make streaks with this wire over a series of tubes of serum. For greater security, this fragment of the colony may be first diluted in the tube of sterilized bouillon, and a drop of this sown in the form of streaks upon serum. These tubes, placed in the stove at 37° C., give at the end of twenty-four hours colonies of which most, if not all, contain the Loeffler bacillus in a state of absolute purity.

When the tubes of serum directly sown with the débris of a false membrane contain numerous colonies of Loeffler's bacillus, the existence of diphtheria may be affirmed; but if the colonies are very scanty —three or four in all, for example—it will be neces-

sary to have recourse to the inoculation of the bacillus in the guinea-pig, for possibly the specimen may be of the pseudo-diphtheritic variety. I shall return to this point farther on.

The bacillus of diphtheria is a rod, straight or curved, always immobile, almost as long as the tubercle bacillus and twice as thick; such is the aspect which it presents in recent cultures on serum or gelose. It then stains very well with Loeffler's blue. When the cultures are older, it takes the Loeffler stain more unevenly. Cultivated in bouillon, the bacilli of diphtheria are grouped in little masses, of which the rods are often arranged parallel to each other, and often present forms of involution just as in the false membranes of diphtheria—though they are shorter, more stunted, some are swollen at their extremities, pear-shaped or club-shaped. Their rounded extremities stain very strongly. But we are not dealing here with spores, for a temperature of 60° C. suffices to kill all these cultures.

In cultures on gelatin, the bacilli do not at all resemble the forms I have described; they are fusiform, roundish, resembling large cocci. Moreover, transported from the gelatin or bouillon to serum, they assume the aspect which they usually present in these media.

The diphtheritic bacillus stains well with anilin dyes, and particularly with Loeffler's or Roux's blue; it stains intensely by Gram's method.

In all media this bacillus develops badly below 20° C., and not at all above 40° C. The most favorable temperature is between 33° and 37° C.

On gelatinized serum, at the end of eighteen hours the Loeffler colonies have the aspect which I have already described. Confluent, they form a grayish stria. Isolated, they present themselves under the aspect of little round spots, of grayish-white color. Soon they extend, become salient, with centre thicker than the periphery. At the end of four or five days they may attain a diameter of three to five millimeters, and are thick, whitish, opaque, with shiny surface. When the bacilli have been sown on serum prepared according to Loeffler's method, they grow still more quickly, for in two days a colony may acquire a thickness of one millimeter and a diameter of five millimeters.

The cultures on gelose grow less rapidly than on serum, especially when the bacillus is taken directly from a false membrane; but the colonies present a characteristic aspect, they often spread considerably, and their contour is not perfectly round. They are white, the centre much thicker than the periphery, and take a grayish coloration when the cultures are sufficiently old.

Veal broth constitutes an excellent culture medium for the bacillus. The cultures form little scales on the sides and at the bottom of the flask; the broth, after its first access of turbidity, regains its original

clearness, and when the cultures are kept in the stove at 37° C. a part of the colonies form a pellicle on the surface of the liquid. After several days of culture, the broth, first alkaline, becomes acid and continues so for a fortnight, then regains its alkaline reaction (*i. e.*, if exposed to free air; otherwise it continues acid).

The bacillus does not develop on potato, and rapidly loses its virulence on glycerized broth (which soon becomes of exaggerated acidity) and in glycerized serum (which takes on an acid reaction not observed in ordinary serum). The bacillus grows in milk, and does not coagulate it. Pricked into gelatin, the development goes on poorly; little spherical colonies adhere the one to the other along the track of the wire; at the end of a long time the cultures spread over the surface of the gelatin in the form of a thin whitish pellicle.

Since the time of Bretonneau the attempt has frequently been made to inoculate diphtheritic membranes in animals, with the intent of reproducing the disease. The results obtained have not been conclusive. But from the day when the bacteriologist found out how to isolate the bacillus from the false membrane, with always the same characters as above described, and was able to cultivate it, innumerable attempts have been made to reproduce the principal features of the disease by means of inoculation with pure cultures of the specific microbe. The results have not been disappointing.

By excoriating the mucous membrane of the pharynx of hens and pigeons, the conjunctivæ of hares, or the vulvar mucous membrane of the guinea-pig, and spreading over the excoriated surface portions of the colonies of Loeffler's bacillus by means of a platinum wire, false membranes are obtained quite like those which occur in man. They are also easily obtained by painting the blistered skin of a hare's ear with some of the culture-liquid.

By inoculating in the same way with the diphtheria bacillus the trachea of hares or of pigeons previously tracheotomized, symptoms resembling croup are easily reproduced. The difficulty in breathing, the noise which the air makes in passing through the obstructed trachea, the aspect of the trachea congested and lined with false membranes, the œdematous swelling of the glands of the neck, render this resemblance actually striking. Death is very frequent after these inoculations; but when the animal resists, motor troubles may follow resembling the diphtheritic paralysis of man.

By injecting one cubic centimeter of diphtheria culture in the marginal vein of the hare's ear, one often produces similar paralysis, should the animal live long enough. Sometimes it is a rapid paralysis extending to the whole body, and fatal in a few hours; sometimes a paraplegia of the posterior extremities, invading the whole body in a day or two, and killing the animal by arrest of respiration and of the heart.

In animals thus inoculated, the autopsy generally reveals, along with fatty degeneration of the liver, swelling of the glands and congestion of the abdominal organs—an acute nephritis which explains the albuminuria noted during life. Lastly, in animals, as in the diphtheria of man, the bacillus poisons the organism and does not infect it. Loeffler has never found the diphtheria bacillus anywhere but at the point of inoculation. Roux and Yersin have multiplied experiments to control this important fact. With one exception, that of the guinea-pig inoculated in the subcutaneous cellular tissue of the abdomen, they have never found the specific bacillus except in the œdematous fluid and false membranes which develop at the point of inoculation. When the bacillus is sown in the blood, in the visceral parenchyma, or in pleural effusions, the result is *nil.* Sixteen hours after the intra-venous injection of Loeffler's bacillus in the hare, no more trace of it is found in the blood or in the organs. And at the same time the disease pursues its course, and the animals under experimentation die in the course of thirty-six hours.

To sum up: A bacillus has been isolated which is found constantly in the false membranes of diphtheritic patients. Inoculated in animals, it reproduces false membranes identical with those of diphtheria, all the symptomatology of croup, paralysis, and albuminuria. This bacillus produces its effects first by an infection, which is and which remains

local, but it rapidly develops a general intoxication of the organism. And if it be objected that the rapidly invading paralysis provoked in the hare resembles only a rare form of the diphtheritic paralysis, we may here anticipate the results to be studied later on in connection with the diphtheritic poison, and remark that Roux and Yersin have succeeded in producing in the dog limited paralysis with slow course, identical with that commonly observed in man as the effect of diphtheria. So many accumulated proofs forbid doubt; and bacteriolgy has completely triumphed in its contention of the specificity of Loeffler's bacillus.

This bacillus is pathogenic to a great number of animals. Rats and mice are completely refractory. The guinea-pig is peculiarly susceptible; a few drops of culture-broth injected under the skin of the belly rapidly kill this animal. At the autopsy we always find these lesions: gelatinous œdema at the point of inoculation; false membrane more or less extensive over the place where the skin was pricked; congestion of the internal organs and of the glands, but especially of the suprarenal capsules; serous or serosanguinolent effusion in the pleural cavities; sometimes splenization of the lungs. Blood from the heart and internal organs, or even some of the pleural exudation, will not yield cultures when sown on serum; but a fragment of the false membrane from the point of inoculation will produce a luxuriant growth. These bacilli may, moreover, be microscopically detected

immediately after the autopsy in the liquid or membrane obtained from the place of puncture. What is a little singular, the microbes will be much less abundant than in the false membranes of human diphtheria; the animal is, in fact, more refractory to the microbe than is man. A marked attenuation of virulence is noted in transmitting the diphtheria from guinea-pigs to other guinea-pigs.

The death of pigeons and of hares inoculated under the skin is much less rapid and constant. Pigeons and hens resist more or less according to the virulence of the bacillus and the quantity of culture inoculated—in general, a fifth of a cubic centimeter of diphtheria culture is the maximum dose which they can support without succumbing. Pigeons which die, exhibit at the autopsy only œdema and a pseudo-membranous product at the point of inoculation, and congestion of the internal organs.

On the contrary, little birds are of all animals the most sensitive to the action of the bacillus of diphtheria.

It requires 2 Cc. of culture in broth to kill a hare by subcutaneous injection. The teguments become œdematous at the point of inoculation, the animal lies motionless, refuses food, and dies in four or five days; there is then œdema at the level of the prick, with hæmorrhagic suffusions of the cellular tissue; glandular, omental, and mesenteric congestions are also observed, with little ecchymoses along the

blood-vessels, and always the characteristic lesion of the liver, the yellowish tint due to fatty degeneration.

In the dog, which also succumbs to subcutaneous inoculation of the diphtheria bacillus, the same local œdema occurs at the point of injection; the animal is paralyzed, lies motionless, and presents the signs of an intense jaundice. The autopsy reveals sclerosis and extreme hypertrophy of the liver.

Cats live six to thirteen days after inoculation. They succumb much more rapidly when inoculated with bacilli that have passed through guinea-pigs. The bacilli are found only at the point of inoculation.

Similar experiments, with similar results, have been made on cows.

The vitality of the Loeffler bacillus, both in and outside of the organism, is very great, but diminishes in proportion as the patient advances toward recovery. When the false membrane disaggregates, becomes softer, it is a sign that it is invaded by common microbes, and that the specific microbe has disappeared. But it is exceptional that we observe the complete disappearance of the Loeffler bacillus so long as the pseudo-membranous exudate lasts.

The presence of the microbe of diphtheria in the mouth is not necessarily always accompanied by the presence of the pseudo-membranous production in the bucco-pharyngeal cavity. In a case of hypertoxic diphtheria supervening in the course of typhoid

fever, in the service of Cadet de Gassicourt, it was found by serum-cultures that the mucus of the throat contained a great quantity of extremely virulent bacilli of diphtheria, while at the same time only a very small lenticular pseudo-membrane was discoverable, and this disappeared in the course of a few hours and was not reproduced; there was no croup. The diphtheria bacillus is found in the saliva of children affected with croup, where no false membranes have appeared in the throat.

When the false membrane has disappeared, and the patient has recovered, often the specific bacillus may be found in the mouth for a week or more, and colonies obtained therefrom are virulent for animals inoculated. Hence convalescent patients may be a source of danger to persons who come in contact with them; it is not known how long after recovery this bacillary survival lasts. Researches thus far made have pertained to children treated in the hospital and subjected to rigid antisepsis of the mouth and throat. But we have no means of determining the duration of the resistance of the bacilli in cases where this antisepsis has been imperfectly performed. Here is a field for future inquiry. Possibly in rare cases the bacillus may long remain a harmless tenant of the mouth, though awaiting a suitable occasion to initiate a recurrence of the malady.

In serum cultures the bacillus lives much longer. Kept at the temperature of the room, the tubes may

show them active for more than six months. Cultures in bouillon, in closed tubes without air and away from the light, retain their vitality and their virulence for thirteen months. On objects of bedding, in the folds of garments, in the crevices of walls, in the dust of the floors, etc., the bacilli may remain in a dried state for an indefinite time, preserving all their virulence. Dried bacilli placed in a room at 33° C. (91° F.) have remained virulent for three months; they may even support with impunity a dry heat of 90° C. (nearly the boiling-point) for over an hour. A natural inference from all this is the uselessness of dry heat as a means of disinfection in diphtheria. It is noteworthy that a bit of dried diphtheritic membrane folded up and put away in a closed drawer, and kept at the temperature of the room, will yield at the end of five months colonies of the Loeffler bacillus scarcely less abundant than in the first days.

The destruction of diphtheritic virus is effected in various ways. It may be spontaneous, as in the organism, where the bacilli disappear as the condition of the patient improves, or as in old cultures, where at the end of a certain time the bacilli, when sown anew, no longer give rise to cultures. Dried bacilli, kept at the temperature of 45° C. for five days, remain sterile. The desiccated false-membranes, the bacilli of which preserve their vitality for five months, at least, when they are kept away from moisture and light, give negative results when sown in culture media after

being exposed to the air, moisture and the sunshine for a month and a half. Sojourn for a few minutes in moist air at 58° C. always kills the bacilli, and this explains the good results in prophylaxis obtained in the hospitals by disinfection of garments, etc., under high steam-pressure.

The destruction of the bacillus of diphtheria by antiseptic solutions is easily obtained. According to D. Espine, solution of corrosive sublimate 1:8000, of phenic acid 2:100, of permanganate of potash 1:2000, will immediately sterilize vigorous cultures. To determine the value of an antiseptic solution, Chantemesse and Vidal immerse sterilized silk threads first in a culture of virulent diphtheritic bacilli, and then for a few minutes in the antiseptic solution; then the threads are washed in distilled water to rid them of any traces of antiseptic substance that may cling to them, dipped into culture-tubes of pure bouillon, and placed in the dry stove at 37° C. These tubes remain sterile if the antiseptic solution is sufficiently strong.

The mixture which has furnished the best results is the following:

Phenic acid, 5 grammes.
Camphor, 20 grammes.
Glycerin, 25 grammes.

M. Barbier has recently shown that sulphoricinated phenol is still more efficacious.

Unfortunately the results are not so speedy and

complete when we have to do with the human organism infected with diphtheria, for it is by no means easy to reach the specific bacillus in all the anfractuosities of the bucco-pharyngeal cavity.

All the Loeffler bacilli obtained from the throats of diphtheritic patients are not endowed with the same virulence. This is easily proved by sowing, in broth, bacilli taken from a series of specific anginas, and inoculating under the skin an equal portion of these liquid cultures in guinea-pigs of the same weight. These animals will not die at the end of the same time. The guinea-pig constitutes a good test of the virulence of the Loeffler bacillus. After keeping one cubic centimeter of a bouillon culture twenty-four hours in the stove, inject under the skin, and the animal will succumb sometimes before the end of the first day, often at the end of two days, rarely surviving longer. There will be found œdema and an eschar at the point of inoculation. The virulence can be measured if at the same time a guinea-pig, a pigeon, and a hare be inoculated, for the pigeon possesses a resistance to diphtheria greater than that of the guinea-pig, but less than that of the hare.

In fatal diphtherias all the colonies that may be used for purposes of inoculation are very virulent; in the severe but not so malignant forms, the specific colonies become less numerous as the disease progresses toward recovery—while the colonies of the first days are all virulent, later colonies are likely to be

less active, and some even inoffensive to the guinea-pig. In benign diphtherias a still greater inequality in the virulence of isolated colonies is to be observed, but as a general rule the bacilli are less active than in the more grave forms of the disease. Still, in a fairly benign angina very virulent colonies may be isolated; which again proves that the bacillus alone does not create the disease, but that we must make great account of the predisposition and of the secondary infections.

We have just seen that the Loeffler bacillus may normally in the organism present an attenuated virulence, whether in the course of benign diphtherias or at the end of more grave epidemics terminating in recovery. In these cases, instead of killing the guinea-pig inoculated under the skin in one or two days, it kills in four or five days, and sometimes even not at all, causing only a local and curable lesion. This is also sometimes the case when we inoculate very old cultures: the guinea-pigs die at the end of a long time, or even survive. But this is not a true attenuation, for to merit that name the latter should be hereditary; we cannot say of a bacillus that it is attenuated until when, sown anew, it gives a daughter-culture equally attenuated. Now by sowing these old cultures in broth, we may see them recover all their primitive virulence. At the same time, very exceptionally we discover a real spontaneous attenuation in the cultures.

Roux and Yersin have met with two examples in which the cultures, primarily very virulent, gave daughter-cultures of very feeble virulence. They have artificially obtained the attenuation of virulence both in the false membranes and in the cultures. For the false membranes they have employed the combined action of the air and of desiccation. A false membrane is taken from the trachea of a child at the moment of tracheotomy, spread out on a clean cloth, dried in the air, then kept in a drawer. This false membrane, when fresh, contains many bacilli easy to see under the microscope; sown in serum, it gives fine colonies; inoculated in guinea-pigs, it kills them in less than two days. A new sowing made at the end of the fifth month of desiccation furnishes colonies less numerous; pure cultures of these, inoculated in guinea-pigs, prove inoffensive—there is little or no œdema at the point of inoculation.

In cultures the diphtheritic bacilli become attenuated when cultivated in a current of air at the temperature of 39°–40° C., and very soon die. The cultures are made in bouillon by means of Fernbach's flasks, which have lateral tubes through which a current of air saturated with steam at the temperature of the stove is caused to pass. The vitality of these cultures is quite short, but before dying they lose their virulence. All the bacilli are not attenuated at the same time; during a certain period the culture contains both attenuated and virulent bacilli, as can

be proved by separating on serum a great number of colonies, and by testing the virulence of each; day by day the number of malignant colonies diminishes, while the non-malignant augment proportionally.

When the bacillus of diphtheria has been attenuated to a point where it no longer provokes much reaction at the point of inoculation in the guinea-pig, it has thus far been found impossible to reawaken its virulence. Successive inoculations in very sensitive animals, which constitute for many microbes an excellent means of restoring to them their primitive activity, remain here without effect; for very young animals, guinea-pigs or hares, show themselves refractory to the first inoculation. But bacilli having still a slight action on guinea-pigs, associated in equal parts with a very active culture of erysipelococci, have reproduced in the guinea-pig the lesions of diphtheria; and serum-tubes sown with the serosity taken from the point of inoculation have yielded abundant colonies of the Loeffler bacillus, killing the guinea-pigs in less than thirty-six hours.

THE DIPHTHERIA-POISON.

To explain the general symptoms characterizing intoxication by the microbe, we must recognize the fact before mentioned that the bacilli, which remain local and do not invade the economy to any extent, secrete a poison, and that the constitutional disturbances are not produced until this poison is absorbed. It is easy enough to isolate this poison by simply filtering cultures of the Loeffler bacillus through a porcelain filter with the apparatus of Kitasato. The bacilli remain on the filter; the poison passes through with the bouillon. The cultures ought to be at least fifteen or twenty days old, otherwise the bacilli will not have had time to develop a sufficient quantity of poison. Moreover, when you make use of cultures kept exposed to the air (in flasks stopped with cotton), you must wait till the bouillon becomes acid, then alkaline again. At that moment it contains a great quantity of diphtheria poison. As soon as the liquid is completely filtered, take it up in a series of sterilized pipettes, which must then be sealed in the flame of the lamp, and placed for several days in the stove at 37° C., in order to guard against infection of the filtered bouillon by other microbes from without or that may have passed through the filter. When the filtered culture is at least two or three weeks old, and one or two cubic centimeters are injected under the skin of guinea-pigs, the animals will die in a space of

time which varies from twenty-four hours to seven or eight days, according to the age of the culture, and consequently the toxicity of its poison. With very old cultures one-tenth of a cubic centimeter of filtered bouillon will kill a guinea-pig, so strong is the poison. One-fifteenth of a cubic centimeter will sicken guinea-pigs but may not kill them; they then present at the point of inoculation, œdema and quite extensive necrosis of the skin. At the autopsy the lesions are found identical with those produced by injection of the diphtheritic bacillus, only the false membrane at the point of inoculation is wanting. There is the same local œdema at the point of the prick, the same congestion of the internal organs (and especially of the supra-renal capsules), the same effusion in the pleura.

Doses of the filtered bouillon varying from 1 to 4 Cc., in subcutaneous injection, cause the death of the hares in two, three, or four days. Here also the lesions are the same as those produced by the inoculation of the diphtheritic bacillus: local œdema, generalized congestion, sanguineous suffusions, and especially the characteristic fatty liver.

A cubic centimeter of toxic bouillon introduced under the skin of the pigeon suffices to kill it.

Mice and rats, immune toward the diphtheritic bacillus, exhibit the same resistance toward the poison. Two cubic centimeters of the filtered diphtheritic bouillon injected into a mouse will not even

produce necrosis at the point of inoculation. If, however, the liquid be concentrated *in vacuo*, a very large dose in very small volume will kill the mouse. Roux and Yersin, in order to kill a white mouse, had to employ a dose sufficient to kill eighty guinea-pigs.

The results which have been obtained by intravenous inoculation of animals are very interesting. A fifth of a cubic centimeter of toxic bouillon introduced into the circulation of a hare suffices to kill the animal very rapidly. A less quantity is not so speedily fatal, but sometimes produces paralytic symptoms. After having received a larger dose than one cubic centimeter, a dog succumbs more or less quickly. If he survives several days, he emaciates, is taken with vomiting, has icterus, and dies with cirrhosis of the liver and nephritis.

When it is desired that dogs shall not succumb to the intoxication, it will not do to exceed for a medium-sized dog (seven to ten kilogrammes) a dose of three-fourths of a cubic centimeter for inoculation. The animal then emaciates, lies stupid and prostrated, and often at the end of eight to ten days presents symptoms of motor paralysis—a paralysis which is generally incomplete, sometimes affecting all four limbs, sometimes only two, the hind limbs or the fore limbs, and almost always extending to all four extremities. After a short period of aggravation, often accompanied by trembling, the paralysis gradually diminishes, remaining for a time confined to one leg,

then disappears altogether. The paralysis generally lasts from three to four weeks.

The filtered bouillon may with impunity be ingested in great quantity by guinea-pigs and pigeons, while one-half of a cubic centimeter introduced into the trachea of pigeons kills them in four or five days, without any lesion of the respiratory organs.

Such are the results obtained with filtered cultures of Loeffler's bacillus in bouillon. If you treat the filtered bouillon with chloride of calcium in moderate quantity, there forms a precipitate of phosphate of lime, which, when collected on a filter and washed with care, proves to be very toxic, killing guinea-pigs and hares in three or four days by subcutaneous injection, with exactly the same lesions as those produced by subcutaneous injections of filtered bouillon. Hence the precipitated phosphate of lime carries down with it the diphtheritic poison.

If you concentrate *in vacuo* filtered diphtheritic bouillon, and add six times its volume of alcohol, a precipitate forms which contains the poison; the latter is very soluble in water. Roux and Yersin have endeavored to obtain the maximum of concentration possible of the toxic substance. To this end, they evaporated *in vacuo* one cubic centimeter of the active liquid, which gave one centigramme of dried residue. Reckoning out the weight of the ashes and the portion insoluble in alcohol which has no toxic action, there remains a weight of four-tenths of a milligramme of

organic matter. Although most of this is made up of substances other than the diphtheritic poison, this quantity nevertheless suffices to kill at least eight guinea-pigs weighing 400 grammes each, or two hares of three kilogrammes each, or to make very sick and even kill a dog weighing nine kilogrammes.

The formation of the poison is favored by heat, *i.e.*, the cultures which ordinarily take twenty days to elaborate their toxine may produce an abundance in a few days when exposed in Fernbach's balloon flasks to a heat of 55° C. (131° F.) and traversed by a current of air. On the contrary, the preservation of the toxine is better effected in closed vessels, sheltered from the air and light; in such circumstances the filtered bouillon easily keeps all its toxicity five months.

The conditions which hinder the formation of the diphtheria poison or destroy it completely are numerous. In contact with the air the toxic power diminishes little by little; and this action, which is very slow in the darkness, is hastened by solar light. Sunlight alone very slowly destroys the toxicity. Filtered bouillon is also modified by the action of heat. Kept two hours at 58° C. (136° F.) or twenty minutes at 100° C. (212° F.), the filtered bouillon becomes so modified that animals inoculated with the poison long survive, but in the end succumb, after considerable emaciation, marked cachexia, and paralysis of the hind limbs, just like animals that have been inoculated with macerations of the organs or

with the filtered urine of diphtheritic patients. When calcium chloride is added to filtered bouillon, precipitating the poison by the phosphate of lime, it will be observed that the precipitate when dried *in vacuo* acts less quickly on the animals than does the wet precipitate; but, on the other hand, it long resists the action of the air, at a temperature of 70° C. (158° F.), and even a heat of 100° C. (212° F.) in the sea-bath for twenty minutes.

The diphtheritic poison may also be attenuated by acidifying a very toxic filtered bouillon. The poison is the more attenuated, the longer it remains in contact with the acid. The toxicity is almost completely abolished by lactic or tartaric acid; it is diminished, but in less proportions, by phenic acid, boric acid, and borate of soda.

The property which the bacillus possesses of producing the diphtheritic poison diminishes with diminution of its virulence, attenuated cultures producing hardly any toxic substance. Behring and Katasato have shown that the poison is destroyed in the bodies of refractory animals.

Authorities are not yet settled as to the chemical nature of this diphtheritic poison. Roux and Yersin think it to be a compound akin to the diastases. Like the latter, it is modified by heat or by air, and precipitated by alcohol; it easily adheres to precipitates. It, however, differs from the diastases in remaining without action upon sugar and the albuminoids.

According to Brieger and Fraenkel, the poison is not a diastase, but a toxalbumin, resulting from the transformation by the diastase of the albumins of the nutrient fluid. They have isolated this toxalbumin, and give the following formula: $C_{45\cdot35}$, $H_{7\cdot13}$, $N_{16\cdot33}$, $S_{1\cdot39}$, $O_{29\cdot80}$.

Inoculated in hares and guinea-pigs, this toxalbumin kills them in the dose of 2½ milligrammes per kilogramme of the weight of the animal. Sometimes death is delayed for weeks, and even months. The toxalbumin kept in a vacuum may preserve its virulence for several weeks.

Wassermann and Proskauer have reached the same conclusions as Brieger and Fraenkel. They think that the toxalbumin of diphtheria is not a simple body, but that it contains two kinds of substances: first albumoses, then the diphtheritic poison properly so-called united mechanically (not chemically) to these albumoses and endowed with the property of undergoing precipitation with them. This is the secret of the variations observed in the toxicity of the matters designated as toxalbumins, which are found more or less charged with poison, according to circumstances. The toxalbumin isolated by the German chemists is, then, an exceedingly complex body, containing probably great quantities of substances absolutely foreign to the poison itself, since the dried precipitate obtained by Roux and Yersin is a hundred times more toxic to animals than the toxalbumin of Brieger and Fraenkel.

Gameleïa puts forth a new conception, viz., that the diphtheritic toxine is derived from certain constituents of the bodies of the specific bacilli. This author attempts to show by the action of the soluble ferments on this poison that it is decomposable into two substances, one of which produces cachexia in the animals. The reactions place this cachecticizing poison among the nucleins; the primary poison is only a nuclein-compound, it is a nucleo-albumin.

Quite recently, Guinochot, cultivating the Loeffler bacillus in urine free from albuminoid matters, and inoculating guinea-pigs with cultures filtered through porcelain, showed that the animals under experimentation died with the same lesions as the control guinea-pigs inoculated with a culture in bouillon, and that consequently the toxine of diphtheria is not necessarily derivable from albuminoid matters, as affirmed by the German chemists. Moreover, it seems that the toxine itself cannot be an albumin in these conditions, for one cannot find in culture-urine any trace of albuminoid matters by the ordinary reagents (Tanret's test, the biuret test, etc.).

Several attempts have been made during the past few years to render animals immune to diphtheria. Already in 1887 Hoffman had observed that guinea-pigs inoculated with old cultures spontaneously attenuated remained refractory to inoculation with recent cultures certainly virulent. Fraenkel and Brieger have shown that by inoculating guinea-pigs with ten

to twenty cubic centimeters of diphtheritic culture bouillon three weeks old and heated between 65° and 70° C. for one hour, the animal is rendered refractory *to subcutaneous inoculation alone.* The immunity is not acquired during the first few days which follow the protective inoculation, for at this time an inoculation of a virulent culture would be more rapidly followed by death than if there had been no previous inoculation. It is only at the end of a fortnight that the animal may receive under the skin the virulent bacilli of diphtheria. Moreover, if animals be inoculated with the Loeffler bacillus, and immediately or after a few hours again inoculated with cultures heated to 65° and 70° C., the subjects die more rapidly than otherwise. These authors contend that the diphtheritic bouillon contains two principles: a toxalbumin which loses its virulence at 70° C., and a second substance that can withstand higher temperatures and is capable of conferring immunity.

These results do not involve any therapeutic application. I shall only mention the tentatives of vaccination of diphtheria practiced on animals and even on children by Ferran; they were far from being successful. But this is not the case with the experiments of Behring. This savant has succeeded in conferring immunity on animals by different processes: (1) by the method of Fraenkel and Brieger, just stated; (2) by inoculating the animals several times with cultures of diphtheria containing constantly decreasing doses of

trichloride of iodine; (3) by using the pleural exudate found in the cadavers of animals dead of diphtheria; (4) by injecting either trichloride of iodine, or chloride of gold and sodium, in animals already inoculated with the Loeffler bacillus; (5) by making subcutaneous preventive injections with oxygenated water, and then inoculating with the diphtheritic germ. Behring has injected the blood of a guinea-pig thus immunized into the peritoneum of other guinea-pigs; he has been able by this means not only to confer immunity—and an immediate immunity—but he has also succeeded in curing animals previously inoculated with the Loeffler bacillus. He has also remarked that this preservative and curative action of the blood of animals that have acquired immunity is not permanent, but diminishes with time. He thinks that the blood of immunized animals has no microbicide but only a toxicide action; which suffices to explain its effects. In any event, the short duration of the immunity conferred shows plainly that we are not here dealing with a true vaccination, and that the blood of immunized animals has no other properties than those of an antitoxic substance.

Behring has quite recently published a new method of vaccination. The diphtheria bacillus cultivated in bouillon made from calves' thymus produces a very feeble toxine. To prepare this bouillon, take two or three fresh thymus glands, hash them fine, and add an equal quantity of distilled water;

macerate twelve hours in a refrigerator; strain and express carefully. Add to the filtrate equal weights of carbonate of soda and distilled water in quantities sufficient to prevent precipitation in heating up to 100° C. for fifteen minutes. After this the liquid becomes grayish-brown; then filter anew through linen to remove the woolly-like flakes that form; pour into culture-tubes, and sterilize in the autoclave. Sow this bouillon with the virulent Loeffler bacillus. When the toxine is well developed, heat the culture up to 65° or 70° C. for fifteen minutes. By this means you eliminate the toxic principle, and there remains only the vaccinant principle. Then inject into the peritoneum of a guinea-pig 2 (two) Cc. of this heated culture. This injection is to be repeated two days afterward, and then at the end of four days. Nine days after the vaccinant injections, the guinea-pig is inoculated with one milligramme of a very virulent diphtheritic culture, and resists the inoculation, but at the point where the injection was made there will be œdema, then an eschar, in which is found the living diphtheria bacillus. This demonstrates that the immunizing injections have, strictly speaking, an antitoxic, but not a vaccinant, property.

SECONDARY INFECTIONS IN DIPHTHERIA.

We know that in most diseases, to the primary infection provoked by the specific microbe are added secondary infections due to the intervention of other pathogenic bacteria. These bacteria thus contribute to a transformation of the disease, whether by provoking local troubles at the point of inoculation, or by distant complications, or by infecting the entire organism through the circulation, or by poisoning the economy by the toxines when they develop.

It cannot be said, however, that we have yet isolated and studied all the microbes which are met with in the false membranes along with the Loeffler bacillus. Several evidently are pathogenic, but researches have thus far pertained to only a few of them. We know that the *Strepto·occus pyogenes* is found very frequently in the false membranes of the diphtheritic. It is not likely to remain confined to the part affected, but may pervade the entire organism through the blood, or find a lodgment in some distant point. Its association with the Loeffler bacillus may be expected to give rise to the hypertoxic forms of diphtheria, veritable septicæmias, in which the microscope shows the presence of the streptococcus in the blood of every part. This streptococcus is found in a state of purity in the suppurations which sometimes accompany diphtheria. It has been found in the otites, the adenites, the phlegmons of the neck,

the suppurations of the trachea consecutive to tracheotomy, the arthrites, and even in mediastinitis accompanied with pleurisy and pericarditis. This microbe has been especially studied in diphtheritic broncho-pneumonias, where it has been found associated with the Talamon-Fraenkel pneumococcus, and where it seems to play the principal rôle. It has also been detected in the vegetations of endocarditis supervening in the course of diphtheria. Lastly, it may give rise to a grave erysipelas, which will make the prognosis sufficiently gloomy.

Not so well known is the rôle of the staphylococcus (*aureus* and *albus*) which has also been found in the false membranes and in the air-passages and lungs affected by broncho-pneumonia, along with a certain number of cocci not yet classified.

This is about all that we know as to the secondary infections of diphtheria; and I shall have finished this division of the subject when I have said that the Loeffler bacillus confers no exemption from the contagion of measles, scarlet fever, and whooping-cough.

THE PSEUDO-DIPHTHERITIC BACILLUS.

In his first researches on the bacillus of diphtheria, Loeffler found this bacillus with all its morphological characters in the saliva of a healthy child. In a second memoir, he describes a bacillus found in the pseudo-membranous products very like the specific bacillus, but differentiated by certain characters of its cultures, and especially by the absence of all pathogenic action on animals. Since then, this bacillus has been well studied by Hoffmann, Zarniko, and especially by Roux and Yersin. When several tubes of gelatinized serum are sown in streaks with false membranes, especially if these are taken from a case of benign diphtheria, we sometimes find in the midst of numerous colonies of very virulent bacilli one or more colonies which produce no effect on animals by inoculation. If you sow on serum in the same manner mucus taken from the throats of patients affected with anginas not diphtheritic (rubeolic angina especially) you will sometimes observe in one of the tubes sown (and generally in not more than one) several rare colonies of bacilli offering all the characters of the diphtheritic bacillus except its virulence. Inoculated in animals, they are inert.*

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*Among the distinctive features of this pseudo-diphtheritic bacillus is its rarity. Out of several tubes sown with diphtheritic membrane, you will find scattering colonies of the pseudo-bacillus in only one or two; in the sore-throat of

The pseudo-diphtheritic bacillus stains like the virulent bacillus by the Loeffler blue, by Roux's blue compound, and by the method of Gram. When the process is examined under the microscope, it will be seen that the bacilli undergo the staining uniformly, or else appear granular, the staining matter having an elective action upon certain points. The bacillus is a rod, straight or curved, with roundish (sometimes swollen) extremities, quite like the diphtheria bacillus, but (according to Loeffler) not quite so long. Sown on serum at 37° C., the pseudo-diphtheritic bacillus yields vigorous colonies, growing as quickly and presenting the same appearance as those of the specific bacillus. On gelose the aspect of the colony is identical with that of the diphtheritic bacillus, but there is difference of growth which is sufficiently marked, especially at a moderate temperature, in favor of the former. When cultivated in bouillon, the pseudo-diphtheritic deposit is thicker and whiter than that of the virulent bacillus, and the bouillon remains alkaline instead of becoming acid (Zarniko). Roux and Yersin dispute this latter point; both bacilli, they say, render the bouillon acid, then alkaline, but the change of reaction is more speedy in the case

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measles, it is seldom that these bacilli are found in any abundance, and the inoculation test shows them to be relatively harmless. Recently Ortmann found this pseudo-diphtheritic bacillus in a case of purulent meningitis associated with the pneumococcus.

of the pseudo-diphtheritic bacillus. The cultures of the latter on gelatin at 20° C. are more abundant than those of the Loeffler bacillus, and the latter grows more abundantly in a vacuum than the former.

Moist heat kills the pseudo-diphtheritic bacillus at 68° C. in ten minutes; just as it does the Loeffler bacillus. Animals the most sensitive to the diphtheritic virus resist inoculation with the former; nothing at the most is seen but a little œdema at the point of inoculation in guinea-pigs; the most marked œdemas being caused by the bacilli from rubeolic anginas. Likewise inoculation by its filtered cultures is generally inoffensive, though large quantities cause emaciation and finally death.

Many authorities admit, with Loeffler, that the inoffensive bacillus is very similar to the virulent bacillus. They base their differentiation on the points I have mentioned: the pseudo-diphtheritic bacillus is shorter, cultivates more vigorously and at a lower temperature in different media, and grows more sparingly in a vacuum; if its cultures in bouillon at a given moment present the acid reaction, this reaction lasts but a short time; lastly, neither the bacillus nor its filtered cultures are found virulent to animals.

These differences do not seem to Roux and Yersin sufficient to carry conviction. They say they have seen the benign bacilli yield, for the first few days, cultures as poor as those of the virulent bacillus. Moreover, abundance of culture has never sufficed to

characterize a microbe. The morphological differences are so feeble that they prove nothing. There remains the question of virulence. But these authors have carried on the attenuation of virulent cultures placed at 40° C. in a current of air, and these cultures became inoffensive to animals, whereas previous to attenuation they would have been sure death. Nay, more, these attenuated bacilli take on in cultures the characters of the pseudo-diphtheritic bacillus; they grow better than the virulent form in the air and at a low temperature, and not so well, on the contrary, in a vacuum. Lastly, when a large quantity of their filtered culture is injected into guinea-pigs, these animals grow thin and cachectic, sometimes even die at length—a result just like what we get with massive doses of the filtered culture of the pseudo-diphtheritic bacillus.

The demonstration would be complete if Roux and Yersin had succeeded in rendering virulent the pseudo-diphtheritic bacillus. Unhappily, all their tentatives in this direction have been in vain. Despite this failure, they are disposed to affirm the identity of the two bacilli. "Under the influence of an eruptive fever or of some unknown microbian association, the pseudo-diphtheritic bacillus takes on virulence and becomes the active diphtheritic poison. This is only a hypothesis; but as we have proved that the virulent bacillus of diphtheria may be attenuated so as to be indistinguishable from the pseudo-diph-

theritic, it is not unreasonable to suppose that this pseudo-diphtheritic bacillus plays a rôle in the etiology of diphtheria. It is still very difficult to define the rôle. Most cases of diphtheria are surely due to direct contagion, whether by means of fresh or of dried virus; but alongside of these diphtherias coming directly from a virulent bacillus, there probably exist some which have for their origin this pseudo-diphtheritic bacillus, parasite of so many mouths. Becoming virulent through conditions which we cannot yet explain, it may be the starting-point of new contagions. The idea that a saprophyte microbe may become pathogenic has been introduced with authority into science by the experiments of the laboratory of Pasteur on the attenuation of virus and its return to virulence. It was set forth in a note by Pasteur, Chamberland, and Roux in 1881; since then it has been accepted by many *savants*, and we think it a fruitful notion which explains many facts otherwise inexplicable."

FALSE DIPHTHERIAS.

Writers have long discussed the nature of certain pseudo-membranous products which objectively are confounded with the diphtheritic false-membrane, but differ by the concomitant symptoms and by the course of true diphtheria. Such is the grayish exudate which is found on inflamed wounds and ulcers, on blisters badly treated, on patches of intertrigo that have been irritated; such are the false membranes of the so-called diphtheritic form of puerperal fever, the pseudo-membranous products which sometimes extend over the infectant chancre or secondary syphilides, those which cover the lips of children affected with measles, which supervene in the course of simple anginas, and especially at the onset of scarlatina.

Bacteriology alone can settle any doubt in this matter by showing that these false membranes do not contain the Loeffler bacillus. It is probable that there are several bacteria capable of provoking fibrinous exudations which undergo organization into false membranes. Among these are the golden and white staphylococci, the streptococcus *pyogenes*, and the Talamon-Fraenkel pneumococcus. Experimentation has shown that with the streptococcus *pyogenes* found in puerperal diphtheroid patches, in certain anginas with suspicious pseudo-membranous exudates, and in the early pseudo-diphtheritic anginas of scarlet fever, we may succeed in reproducing false membranes of

considerable extent and toughness upon the excoriated mucous membrane of the beak of pigeons. I have also isolated the staphylococcus *aureus* from the white, thick patches adherent to the stomatitis of patients suffering from measles. Lastly, I have found the pneumococcus in pseudo-membranous angina and laryngitis.

All these affections, where the Loeffler bacillus is wanting, merit the name of false diphtheria. With diphtheria they have nothing in common but the false membrane, and they are distinguished by the absence of the characteristic intoxication which the specific bacillus produces. We shall study them more completely in connection with the diagnosis of diphtheria.

ANIMAL DIPHTHERIA.

There exists in several species of animals, notably in birds, a disease characterized by a false membrane very like that of human diphtheria. This sometimes appears in the trachea, causing asphyxia, with stridulous breathing similar to that of croup. This aviary diphtheria is believed by some writers to be identical with the malady as found in man. These writers point to the frequent coincidence of epizoötic pseudo-membranous diseases among fowl with epidemics of diphtheria among men, and the undeniable fact of the experimental infection of pigeons and other birds by the Loeffler bacillus, the ensuing malady exhibiting the main features of the disease as it prevails naturally among birds. But these statements of contagion have been disputed, and numerous instances in contradiction have been given. Let us see what data we actually possess respecting animal diphtheria.

Competent observers have noted pseudo-membranous affections in birds, cattle, hares, cats, sheep, and hogs. The diphtheria of birds attacks chiefly pigeons, hens, pheasants, and some wild birds. It is epidemic and contagious; is often met with in barnyards and henneries, where it decimates the fowl; is characterized by false membranes about the beak, mouth and throat, the nares, the larynx, and sometimes the intestine. The malady may localize itself

in one patch, or may spread and even invade the entire mucous tract. There exists a visceral form of this affection, with fibrinous deposits resembling, at first sight, miliary tuberculosis. You may even reproduce all these forms by applying to the different mucosæ the virulent matters of aviary diphtheria. The most frequent and best known form is that commonly called *the pip*. This exhibits grayish false-membranes covering the tongue, throat, nasal fossæ, and finally obstructing these passages by its exuberance. When this exudate is removed, the mucosa is seen to be eroded underneath; but the false membranes are speedily reproduced. The bronchi or the conjunctivæ may be secondarily invaded. On palpating the cutaneous surface, you often discover little fibrinous nodules. This disease often lasts days, weeks, and even months.

Megnin has described a latent form of the diphtheria of pigeons, in which the adult birds preserve all the appearances of health and have only little diphtheritic pellicles in the œsophagus, but may transmit a fatal diphtheria to their young. The prognosis is grave, without being necessarily hopeless. There are numerous little cutaneous tumors containing a yellow fibrinous matter of caseous aspect. False membranes invade the conjunctivæ, the nares, the trachea, and even the intestine. Below the exudate, there is congestion of the mucosa and infiltration of the subjacent parts.

Aviary diphtheria attacks young birds especially, it is transmissible to other animals, notably cats.

The specific microbe of aviary diphtheria is a rod resembling that of human diphtheria, but somewhat shorter, with extremities not swollen. It grows on gelatin at 17° or 18° C., and does not liquefy the gelatin; its colonies spread widely on the surface of the gelatin. On potato it gives a thin, grayish culture. Loeffler inoculated four pigeons with this bacillus; he obtained inflammation at the point of inoculation, and a false membrane. Two of the pigeons died, and the bacillus was found in the lungs and liver. This bacillus is less active than that of human diphtheria in the hare, the guinea-pig, and the dog. Injected into hens, it produces only lenticular spots at the point of injection, without general empoisonment. Hence Loeffler thinks that the diphtheria of hens is not identical with that of pigeons.

These researches have been confirmed by Babes, Puscariu, and Krajewski.

Recently Haushalter isolated from the false membranes of hens affected with diphtheria, a bacillus which he considers as the specific agent of aviary diphtheria. Morphologically this bacillus resembles that of tuberculosis, but its length is variable. It does not liquefy gelatin. On gelose at 37° C. it forms a membranous elevation, white and smooth. It develops well at 37° C. on gelatinized serum; and gives rise to a grayish, moist, elevated papule on

potato at 37° C. The sown bouillon rapidly becomes turbid, and deposits a powdery sediment.

The injection of these cultures into the blood of the hare, provokes diarrhœa and fever; the animal, however, recovers. Subcutaneous injection of the bacillus provokes suppuration. Inoculated in the pectoral muscle of a pigeon, it kills in less than forty-eight hours, and the bacillus is found in the blood. This bacillus is also pyogenic to hens.

Bovine diphtheria is quite common in Germany, though unknown in France. It constitutes veritable epizoötic epidemics. The animal is taken with extreme lassitude, with fever and prostration, has rigors, refuses to eat, and rapidly emaciates. There is an abundant flow of saliva; the snout is wide open; the tongue hangs out of the mouth and is almost always swollen. The swelling extends to the whole of the buccal mucosa, which is covered with yellow patches of exudation penetrating deeply into the mucosa, which is often eroded. These false membranes often have a thickness of one and a half centimeters. The pituitary, laryngeal, and tracheo-bronchial mucosæ may be invaded in their turn; then there is a yellowish discharge, the respiration is labored and stertorous; there is sometimes pneumonia or pleurisy. The exudate is seen on the conjunctiva, in the interdigital space, and about the sheath. Often the animals are affected with pseudo-membranous enteritis, which manifests itself at first by constipation with hard

fæces covered with false membranes; then diarrhœa sets in, sometimes dysentery, almost always followed by death. The laryngo-pharyngitis, though less fatal than the enteritis, kills not less than four animals out of five. At the necropsy you will note œdematous infiltration below the mucous membrane which is covered with false membranes, and pseudo-membranous nodules in the skin, cellular tissue, muscles, liver, and lungs. The latter are often hepatized, sometimes gangrenous.

The virulent agent of this disease exists in the false membrane, the nasal discharge, and in the diarrhœal liquid. With these products a pseudo-membranous affection may be provoked in calves, birds, hares, and sheep. Loeffler has examined the false membranes of the buccal cavity in seven cases. On preparations stained with alkaline methylene blue the superficial stratum stains strongly with blue; below this there is a large zone unstained; then the deep layer forms a colored band. The first stratum contains a great variety of micro-organisms, especially cocci; in the deep part are seen bacilli united in long undulating filaments. These bacilli measure half the length of those of charbon; Loeffler considers them specific in bovine diphtheria.

There exists in cats a disease characterized by dysphagia, inflammation of the palate and throat, and dyspnœa. The conjunctiva is sometimes red. The animals emaciate, cough, and have bronchial catarrh.

Most cases recover, but the disease may last a long time. In one case there was paralysis of the hind limbs. Klein says the disease is transmissible to man. He found false membranes in the trachea and bronchi in three cases. Sections of this exudate stained showed in only one instance bacilli resembling the Loeffler bacillus; in the other two cases, where death was late, he found no bacillus. Sowings on various culture-media remained sterile. These facts are clearly insufficient to identify human diphtheria with the diphtheria of cats.

Ribbort has studied in the hare a disease which produces acute fibrinous peritonitis, with swelling of the mesenteric glands, and characterized chiefly by the lesions of pseudo-membranous enteritis in the large and small intestines. He has isolated from the false membrane a bacillus 3 to 4 μ long and 1 to 1 μ 4 broad, which grows well in gelatin without liquefying, and forms grayish colonies on agar and on potatoes. Subcutaneous inoculation of this bacillus determines a sort of septicæmia in the hare; in the throat it develops false membranes on the tonsils.

In dogs there is often a sort of pseudo-membranous angina or stomatitis which is very grave, with fever, dysphagia, flow of saliva, and general enfeeblement; death supervenes at the end of five or six days.

Hogs are also subject to a pseudo-membranous affection.

These affections have not yet been studied from a bacteriological point of view.

SYMPTOMS.

Incubation.—When the Loeffler bacillus has penetrated the economy, before its presence is manifested on the mucous or cutaneous surface by local symptoms, and before its toxine has given rise to general symptoms, a variable time intervenes during which the infection remains latent; this is the incubation period. Statistics prove that the duration of incubation is generally from one to three days, but exceptionally from twelve to fifteen days. Experiments on animals have indicated that the time which elapses between inoculation and the first manifestation of the disease is proportionate to the quantity and virulence of the virus injected. It is probable that the soil on which the infection develops, and the resistance of the organism, play an important rôle, of which it is still impossible to measure the value.

Clinical Study of Diphtheria.—We know now how the Loeffler bacillus acts on the organism; it fixes itself and forms colonies on the eroded mucous membrane or denuded derm, and produces a false membrane there, where it lives confined, developing and multiplying outside of the organism. To these local manifestations are joined general accidents, functional troubles of organs remote from the point of infection. No one has ever found the Loeffler bacillus in the blood or viscera; we must then refer these general disorders to the systemic poisoning

by the products of the diphtheritic bacillus, and to similar infections by other pathogenic bacteria whose association complicates the disease or may even completely alter the clinical aspect. We know that the diphtheritic poison penetrates the circulation; it is easy to demonstrate this, for the urine of the patients contains a notable proportion of this poison; and if we inject this urine in animals we produce in them lesions identical with those which are consecutive to inoculation with the Loeffler bacillus or with the filtered bouillon. This poison fixes itself in most of the organs—the liver, the spleen, the kidneys, the heart, the nervous system, etc.; for a maceration of these organs injected into guinea-pigs and hares kills them, with all the lesions characteristic of diphtheria. It is certainly to the toxine that we must refer the alterations noted in these organs in diphtheritic patients, for no bacteria are found there. This is not the case when certain complications exist, such as the suppurations, the broncho-pneumonias, which are often superadded to the diphtheria; we have seen that these owe their origin to new infections by microbes other than the Loeffler bacillus.

It will be convenient to consider this subject under three heads: the first comprises the symptoms of bacillary infection; the second, those of systemic poisoning; the third, the complications due to secondary infections.

Diphtheria sometimes begins by local, sometimes

by general, symptoms. In the latter case, the Loeffler bacillus has already been multiplying in an infected point, but has not yet produced the false membrane. Often, also, the disease is announced by symptoms at once local and general. The onset may be sudden, with great gravity, or slow and insidious. In children it is not rare to see diphtheria begin suddenly with a high fever, with a temperature of 40° C., and often with chills, vomiting, delirium, and convulsions, lividity of the skin, etc.; and it may be only accidentally that attention is directed to the throat.

I. Symptoms of Bacillary Infection.—Diphtheria manifests itself by the development of a false membrane, at first thin, whitish, opaline, of rather softish consistence. This membrane may be seated on a mucous membrane or on any part of the skin; it is met with, in order of frequency, in the throat, larynx, nares, trachea, bronchi, mouth, Eustachian tube, middle ear, conjunctiva, prepuce, glans penis, anus, scrotum, and uterus; is extremely rare in the œsophagus, stomach, and intestine. In the stationary period of the disease, the false membrane is firm and elastic; may generally be detached in large flakes with an ordinary swab or with forceps. Below, the mucosa or derm is rarely ulcerated, but bleeds easily. If a removed shred of the pseudo-membrane be agitated in a glass of water, it will not dissolve. The false membranes form at points where they give rise to little lenticular concretions, or oftener to exten-

sive circular patches or strips. Often they take the form of the organ on which they rest: the larynx, the Eustachian tube, etc. Exceptionally they have been known to take on extraordinary dimensions—in one instance, covering the skin from the neck to the sacrum. At first smooth, they soon become rugous; their surface is grayish, sometimes yellowish, or it may be brown, colored by the blood, and resembling a gangrenous eschar—in very grave forms the fetid odor of the latter is noted -- the consistence being pulpy, and the exudates forming a putrid and sanious magma. When the diphtheritic patient recovers, the false membrane softens, disintegrates, and disappears.

One of the principal characters of the false membrane is its ability to reproduce itself repeatedly. When it is removed, the mucosa underneath remains at first bare, but in the course of a few hours the fibrinous exudate is re-formed; and this process will go on as long as the disease lasts. The false membrane has also the property of being essentially invading; it rarely remains localized to the point where it first forms, but spreads to contiguous regions; starting in the throat, it ascends the nasal fossæ, or spreads downward into the trachea.

The particular seat of the false membrane determines in some measure the concomitant local symptoms. Diphtheria usually begins with a sore throat. There is nothing at first to excite alarm: a little redness and swelling of the velum pendulum

and tonsils; a sensation of dryness in the throat (there is yet no false membrane—it is the congestive period). After a few hours the mucous membrane exhibits a thin coating of mucus, partly concrete, which soon changes into an opaline patch, half transparent, but little adherent; this is the false membrane. From the first, there is a notable engorgement of the submaxillary glands, which become larger as the disease progresses. The false membrane is first seen on one or both tonsils; it may invade the soft palate or uvula, or extend to the nasal fossæ and larynx. The pain generally remains slight and supportable; but the dysphagia, which was scarcely noticeable at first, generally augments as the false membranes extend. The voice takes on a nasal twang. The respiration is a little oppressed when there is hypertrophy of the tonsils, and especially when there is coryza.

At whatever point the diphtheria develops, it always presents the local symptoms of an ordinary inflammation, with this phenomenon superadded: the formation of a false membrane. But when the disease invades the air-passages, it adds a new element to the symptom-picture and a factor of gravity to the prognosis: the mechanical obstacle which the false membrane interposes to respiration.

In most cases, croup is preceded by a diphtheritic angina, and supervenes upon the latter in the course of the first week of the disease; sometimes all the characteristic symptoms appear from the very

onset. In primary croup, the laryngeal symptoms appear in the midst of apparently perfect health, or follow a slight cold or catarrh of the bronchi. Exceptionally, the croup is ascendant—the bacillus having primarily affected the bronchi.

It is customary to describe three periods in the progress of croup:

(*a*) Period of Invasion: The patient complains of a little pain in the region of the trachea, speaks in a hoarse voice, and has a loud, hoarse, barking cough. More rarely the onset is sudden, as in stridulous laryngitis; a child, only a little hoarse the evening before, is awakened in the middle of the night by violent attacks of a hoarse, resonant cough; quiet follows, but the respiration gradually becomes difficult and interrupted. This first period may last several days, but sometimes the paroxysms of suffocation come on at the end of several hours, or even at the onset.

(*b*) These paroxysms characterize the second period; the voice and cough are extinguished; dyspnœa becomes constant, with frequent attacks of suffocation; the latter come on sometimes spontaneously, without apparent cause, but sometimes are excited by emotion. All at once, with pale face and wild, staring eyes, the child starts up in bed in the anguish of suffocation—clings to the bed-post—and, with head thrown back and mouth wide open, dilates the thorax to its utmost. Inspiration is whistling, convulsive, painful, prolonged; expiration generally slow and

laborious. At times, the child in coughing clutches at its throat, as though trying to rid itself of the object that is causing suffocation; the countenance all the time becoming livid. The attack lasts ten minutes or so, and may terminate in death. Oftener there is another period of calm, during which the breathing improves, the color comes back, but respiration still remains noisy and embarrassed, till a new attack sets in.

Sometimes there are no paroxysms of suffocation, but the dyspnœa gradually and without intermission becomes worse and worse. The obstacle in the larynx hinders the entrance of air into the bronchi; so when the thoracic cavity dilates in inspiration, the intrathoracic pressure falls; there is a sort of aspiration of the abdominal organs from below upwards; the epigastric hollow is strongly depressed, instead of projecting as in the normal state (substernal suction). As the glottic cleft becomes more obstructed, inspiration will be attended by a second depression at the lower part of the neck above the sternal notch.

This dyspnœa is sometimes temporarily relieved by the expulsion of false membranes, which may show an exact moulding of the bronchial tree. Then the child becomes quiet and somnolent, and ceases to struggle against the asphyxia which is growing more and more pronounced.

(*c*) The third period has now set in. The teguments are cyanosed; the cheeks and lips are purple;

the extremities cold; the patient lies limp, inert, stupid, rousing from time to time when harassed by a paroxysm of coughing, then falling back and surrendering to the progressive asphyxia, and no longer responding to any excitation. This condition frequently yields to a state of complete resolution, very like coma; the patient may die suddenly in a paroxysm of suffocation, or in convulsions. If, as rarely happens, croup which has arrived at this period terminates in amendment and recovery, the cough becomes more noisy and more moist, the dyspnœa diminishes and disappears, but the voice remains long husky.

We shall see further on, that croup does not have the same aspect in the adult as in the child.

Even in benign diphtheria it is a common thing to note a little coryza with serous discharge. But only in the malignant forms is there invasion of the nasal fossæ by the false membrane; there is then redness of the nasal mucous membrane (which is covered with crusts), and a sero-mucous flow, often fetid and sanguinolent, which excoriates the skin of the upper lip; false membranes cover the turbinated bones. The specific bacillus may pass from the nares into the nasal duct, and the pseudo-membranous exudate invade and close the latter, producing a persistent flow of tears. The inner angle of the eye is soon invaded, and the false membrane spreads over the conjunctiva. Ocular diphtheria is, however, quite rare.

At the anus, vulva, or meatus urinarius, the medical attendant will sometimes notice diphtheritic patches, which generally appear secondarily to a diphtheria of the pharynx. Excoriated parts of the skin, lips, and nares, the surface of wounds (especially those of tracheotomy), burns, leech-bites, etc., may be the seat of false membranes. Whenever, in fact, in a diphtheritic patient, you see an erosion of the skin, you should close it immediately by an antiseptic dressing. You cannot be too careful, especially in children, in the employment of sinapisms, for if you obtain a blistered surface you have a new seat of infection to deal with. When diphtheria invades the skin, the excoriated surface first becomes red, then is covered with false membranes. Phlyctenulæ appear around the infected point, break, and in turn become covered with false membrane. Often the affected parts take on a gangrenous appearance. The denuded derm also absorbs the diphtheritic poison, just like the mucous membrane when invaded by the disease.

II. Symptoms of Systemic Poisoning.—From the onset, unless the form of diphtheria be very benign, it is easy to see that the entire organism is smitten. The fever, the extreme pallor (often leaden hue), the general enfeeblement, the glandular engorgement, the albuminuria, the hæmorrhages, are so many proofs that the poisoning follows close on the infection, while the myocarditis and the nervous troubles which

later supervene demonstrate that the poison survives the bacillus.

In the gravest forms the patient lies apathetic, shows an invincible repugnance toward food, and expresses by his features and his aspect extreme lassitude and profound prostration.

The fever is always variable and presents but few indications; is not, in fact, a characteristic symptom. In grave forms it may be *nil*, and in the most simple cases (even at the onset) extreme. Hence a high fever at the beginning should not alarm; has not a long duration, and does not cause depression of the forces. Generally in the first few days the temperature does not exceed 38.5° or 39° C.—that is, it is lower than in an ordinary quinsy sore-throat. It is also rare to note chills at this period.

During the stationary period the temperature varies according as the disease advances toward recovery or death; if the former, the fever persists for several days, then the temperature suddenly or after several oscillations falls to the normal; a fatal termination, on the other hand, is generally preceded by a rising or permanently high temperature—exceptionally, however, the temperature falls below the normal, when the extremities become cold and cynosed and the patient succumbs in complete algid collapsus. If any complication supervenes, the temperature remains elevated or rises again; such ascensions are observed when the false membrane is reproduced or grafts itself

on a new point, or when there is broncho-pneumonia, albuminuria, or paralysis.

The pulse line is more regular than that of the temperature; in general the pulsations are frequent—120 to 140 per minute—and often do not become slower until the temperature has returned to the normal. The more malignant the form of the disease, the more weak and rapid the pulse, though it may in some cases be abnormally small and slow.

The acceleration of respiration is proportioned to the rise of temperature.

The glandular engorgement is constant in diphtheria. The submaxillary, parotid, and supra-hyoidean glands are the most markedly swollen. The glandular tumefaction corresponds to the degree of intoxication; it develops early; the glands are taken singly or in groups; their size varies from that of a hazelnut to that of a walnut; they are painful to pressure, and the skin over them is a little hot and sometimes red. In the malignant forms the glandular engorgement takes on extraordinary proportions; there are then regular diphtheritic buboes; the cellular tissue which surrounds them is infiltrated and blended with the inflammatory mass so that the region is completely deformed. If the cervical glands are the seat of the engorgement, the tumefaction is so considerable that the neck appears larger than the head which it supports. These adenopathies may suppurate by reason of a secondary infection by the pyogenic microbes.

The urine is generally scanty and high-colored, depositing urates copiously; in some cases, however, it is clear and transparent. The average urinary excretion in cases that recover is 300 to 400 grammes in the twenty-four hours; in fatal cases the quantity may fall below 100 grammes, and there may even be complete anuria. Tracheotomy is generally followed by diuresis for two or three days. The density of the urine is always high, without, however, exceeding 1.028 in favorable cases.

Urea is augmented, and rises to 12 and 15 grammes per liter, instead of 10; but in cases that terminate fatally the figure may fall to one gramme per liter.

The urine in diphtheria is albuminous in more than two-thirds of the cases. Albumen may be found from the onset, or, as is oftener the case, from the third day—during all the stationary period, or at the end of the disease. Sometimes its disappearance coexists with a new development of false membranes. Albuminous urine is generally limpid, of an amber-yellow color, rarely bloody. The deposit examined under the microscope reveals lithates and phosphates, epithelium, hyaline or fibrinous casts, and red and white blood-corpuscles. The quantity of albumen varies from a few centigrammes to ten grammes per liter. The albuminuria may be of brief duration, disappearing after twenty-four hours, or it may be persistent, even continuing a month or two. The abundance of

the albumen is generally proportioned to the gravity of the diphtheria, but there is no fixed rule about this. Albuminuria in this malady may be looked upon as an epiphenomenon, which may in a certain measure indicate the degree of intoxication of the organism.

It is rare to see diphtheritic patients present symptoms testifying to a profound renal lesion. The anasarca accompanying the albuminuria is quite exceptional. There may be only a little œdema about the face. Sanné cites a case of œdema limited to the glottis, suggestive of croup. Uræmia is infrequent; when supervening, it takes on the eclampsic or comatose form.

The digestive functions are not disturbed at the onset. Later on, the anorexia becomes absolute and constitutes a serious danger. Vomiting is a rather rare symptom; at the onset or prodromic period it is without gravity, but later it is almost a certain sign of serious complication. During convalescence, repeated vomitings are of unfavorable omen and are often followed by a fatal termination. The vomited matters sometimes (though rarely) contain false membranes from the stomach or œsophagus.

Diarrhœa coming on at a late stage is generally related to a marked degree of intoxication. The stools are then fetid and sanguinolent, sometimes containing the débris of false membranes. The profuse diarrhœas often noted in toxic diphtherias have been compared to the diarrhœa observed in hares

after intravenous inoculation with large quantities of the diphtheritic poison.

Hæmorrhages are tolerably frequent in diphtheria, and are almost always associated with malignant cases. It is especially at the onset that they have been noted, and during the first five or six days. I refer here to the dyscrasic hæmorrhages which are dependent on a profound intoxication of the organism. They take place around the false membranes, the latter being thereby infiltrated and stained brown; the bleeding increases after swabbing the diphtheritic patches. The epistaxis of the prodromal period is sometimes very abundant; there is often spontaneous bleeding from the gums, lips, throat, and even purpura hæmorrhagica has been noted. Hæmorrhages into the nerve centres have been the cause of instant death or hemiplegia. The prognosis of hæmorrhage in diphtheria is very grave.

Cardiac and nervous disturbances characterize the convalescence. Œdema without albuminuria, general or limited to the face or extremities, has been observed from the eighteenth to the twentieth day of the disease. The pathogeny of this œdema is very obscure.

When the local symptoms of diphtheria have all disappeared, and the patient is convalescent, sometimes an attack of syncope supervenes, which is the first grave symptom of a complication previously latent: myocarditis. This lesion generally manifests

itself five, six, or eight days after the onset of convalescence—sometimes a little later, especially in young children. The first symptoms are: occasional palpitations, a little restlessness and dyspnœa, frequent pulse, a state of temporary cardiac erethism; then the pulse becomes feeble, compressible, and soft; the heart-beats are obscure and distant, with intermittences, and there is pain in the cardiac region. In adults this pain may be so severe as to simulate angina pectoris. Most of these symptoms may be overlooked in children until pallor and collapse suddenly supervene. This pallor and cardiac failure are exaggerated on making effort, and the patient is always menaced with syncope. The general enfeeblement continues; vomiting and diarrhœa are sometimes present. The præcordial pain augments and becomes agonizing and constrictive. Children do not, however, complain of this pain so much as adults, for children soon fall into collapse. Whatever may be the age of the patient, he is soon the prey of a very marked paroxysmal oppression; lies prostrate, with face livid, features pinched, lips cyanosed; then suddenly he grows paler, and lies motionless—syncope has taken place.

The pulse is irregular and compressible, with occasional intermittences; the feebleness of the pulsations marks the insufficiency of the ventricular impulse.

The physical signs obtained by examination of

the heart are those of acute dilatation. The præcordial region presents a slight vaulting; you can see the propagation of the cardiac pulsations from the apex to the epigastrium. The apex is generally found in the fifth or sixth intercostal space, outside of the mammary line. The hand, instead of being raised by a single shock, perceives a series of successive undulations and irregularity of the shocks. Percussion indicates an augmentation of the volume of the heart in every direction; but it gives little information in the infant. Auscultation reveals all the types of arythmia possible, with more or less marked obscurity of the sounds of the heart. You may observe tachycardia, bradycardia, a *bruit de galop*, or reduplication of the second sound. Sometimes the first bruit is also reduplicated, and you hear four consecutive bruits. Inversely, one of the two bruits, especially the first, may be wanting.

The state of the heart has been compared to that in animals poisoned by digitalis. As the enfeeblement of the cardiac muscle augments, there arises a soft systolic bruit, loudest at the apex, essentially transitory. This sign is found in most of the acute myocardites. Lastly, the sounds of the heart become more and more muffled and distant, until only a feeble undulation is perceived, which Lancisi called trembling of the heart.

Along with these symptoms of cardiac enfeeblement the general prostration arrives at its maximum.

The teguments are ashy pale, covered with a cold sweat, the extremities cyanosed. The patient lies motionless, the respiratory movements scarcely perceptible. From the onset of the cardiac accidents, albumen reappears in the urine, but the temperature never transcends the normal, and may fall below it in a period of collapse.

Thus it is that diphtheritic myocarditis comports itself: insidious, sometimes fulminant in the child, it follows a progressive course in the adult, who often survives one or perhaps several attacks of syncope; it is, nevertheless, almost always fatal.

Generally from eight to fifteen days after recovery from the local symptoms of diphtheria, the paralysis manifests itself. It may make its appearance earlier, even during or at the end of the first week; then again, it may come on as late as a month or two after the patient has apparently recovered. The rule is that the paralysis comes on during full convalescence. It is a very common accident of the disease—existing, according to Roger, in one-third of the grave but not fatal cases.

The paralysis may follow the most benign as well as the most severe cases. There have been epidemics in which it was a very marked and almost always fatal symptom. It is not so common in children under ten years of age as in adults.

The onset of the paralysis is generally slow and insidious. There is first only a little hesitation of the

motor functions, then deglutition, walking, and other movements become more and more difficult. The paralysis may be ushered in during convalescence by a little febrile rise, or a return of albuminuria.

The point of election of the paralysis is the velum pendulum, where it almost always begins, and where it may remain localized; or it may extend to other parts and constitute the generalized form of the disease.

When localized in the soft palate, the paralysis is essentially insidious. A slight pallor, a little slowing of the pulse, are the only disturbances of the general state which are noted. The paralysis would easily pass unperceived if the reflux of liquid aliments by the nasal fossæ did not indicate the impediment to deglutition. During the second stage of deglutition, the pharynx contracts on the alimentary bolus to seize it and propel it downwards; normally the velum pendulum falls back and closes the posterior nares, but when this muscular septum is paralyzed a portion of the ingesta will enter the nasal fossæ. There is generally at the same time a slight paresis of the upper part of the larynx; the occlusion of the glottis is incomplete, and the patient coughs during deglutition because a few drops of the liquid or particles of food come in contact with the mucosa of the larynx.

If the paralysis of the velum pendulum is complete from the onset or becomes so subsequently, if

the pharynx is paralyzed in its turn, the food can only be swallowed after repeated attempts, which soon fatigue the patient and sometimes lead him to refuse all nourishment. The voice is feeble and nasal, the articulation of sounds difficult, the speech slow; and if the breathing is normal while the patient is awake, it is more or less stertorous during sleep.

When the diphtheritic paralysis does not remain localized, it may begin with the velum pendulum, then extend to the muscles of the eyes, of the upper and lower limbs, of the trunk, of the neck, of the rectum and bladder, to end with the organs of the special senses. This is the ordinary course of the more complete forms of paralysis. More rarely, it may attack the lower limbs before affecting the larynx and the tongue, or even begin with the upper extremities, then invade the velum pendulum and pharynx, and lastly attack the lower limbs.

When the paralysis is thus extensive, grave general symptoms—such as the ashy hue, collapse, restlessness—are often present; sometimes vomiting, severe diarrhœa, convulsions, and sooner or later coma. But these alarming symptoms are only met with in the very grave cases; and with the exception of a little albuminuria and fever at the onset, the constitutional symptoms may be inconspicuous.

We shall follow, in the description of the troubles of motility, the usual order of extension of the paralysis. Generally affecting the entire surface of the soft

palate, it may be localized and only occupy one-half of this organ and the pharynx. If you titillate the base of the tongue or pharynx, you will see contractions on the side that is not paralyzed. The anæsthesia frequently extends to the upper part of the larynx, and this favors the passage of the food particles into the air-passages.

After the velum pendulum, the muscles of the eyes are very often attacked. The muscles of accommodation are paralyzed; the motores oculorum are affected in their turn, and strabismus (which is sometimes temporary) and ptosis of the upper lid are noted. But generally troubles of vision, referable to a fault of accommodation, supervene; the sight is enfeebled in different degrees, from slight amblyopia to complete blindness; there is hypermetropia, mydriasis, and, if but one eye is affected, inequality of the pupils. Almost all of the ocular muscles may be involved in turn.

The lower extremities may be paralyzed immediately after the velum pendulum, and sometimes the paralysis is limited to this double manifestation; oftener they begin to be enfeebled when there already exist ocular troubles. The paralysis of the lower extremities generally takes on the form of an incomplete paraplegia. It is announced by formications and numbness in the legs. Walking becomes uncertain; the patient has an incomplete perception of the ground under his feet, and finds it especially difficult

to go up and down stairs; darkness aggravates these troubles of motility. Then the muscular feebleness augments, and walking becomes very difficult if not impossible; at the same time, the paralysis is never complete. The patients, who are still able to stand, move along by dragging or sliding their feet, as though they were fastened to the ground by an enormous weight. When they are confined to bed, the lower limbs still retain considerable power of movement, but without energy or much reliability — Jaccoud calls it rather an ataxia of movement than a paralysis. Brenner divides these phenomena of incoördination into three classes: (1) True ataxia, caused probably by a lesion of the centre of coördination of movement; (2) ataxic paralysis, characterized by paresis of certain groups of muscles of the limbs and by the more complete paralysis of other muscles; (3) true paralysis, which may attack equally all the muscles of the limbs, and which may be complete or incomplete. These ataxic symptoms, joined to the abolition of the patellar reflex and to the eye-troubles, may give rise to a form of pseudo-tabes.

Contracture is quite rare.

The enfeeblement and even the abolition of the patellar reflex has been often noted. These modifications are seen from the onset of the paralysis, and often survive the latter for some time.

The affected muscles present the reaction of degeneration; there is augmentation of the galvanic and diminution of the faradic contractility.

The hands soon become awkward and clumsy; the patients drop or upset objects that they attempt to handle; the upper limbs are seized with tremblings. Then the muscular enfeeblement augments; the dynamometer marks only a force of 20 kilogrammes instead of 50, and the patient finally becomes so helpless as to be unable to move himself in bed, or to feed himself. Here, too, we find the same enfeeblement of the reflexes, the same reaction of degeneration, as in the lower members.

The muscles of the neck and face may be paralyzed in their turn. The paralysis of the face is rare; it may be complete or incomplete, unilateral or bilateral; in the latter case the features remain motionless, and the visage takes on a stupid expression, although there may be no intellectual trouble. The tongue, the lips, the cheeks, may be affected at the same time; the saliva flows continually from the mouth; the tongue is agitated with fibrillary tremors, and may even hang out of the mouth. The patient speaks with difficulty, and stutters; can neither blow nor whistle. *En résumé*, the paralytic troubles may be united so as to form the labio-glosso-laryngeal syndrome.

Paralysis of the bladder and rectum is also observed. If the muscles connected with the spinal column are affected, the latter is curved forwards, or may be deviated laterally.

In the case of paralysis of the vocal cords, there is complete aphonia.

The heart troubles may be limited to temporary palpitations, tendencies to fainting, to slight irregularities of the pulse, but at other times take on a very grave aspect and manifest themselves by præcordial anguish, cardiac ataxia, slowing of the pulse, attacks of suffocation, and syncope. Henoch divides the cardiac paralyses into three groups: (1) Early paralysis, whose prognosis is very unfavorable; (2) cardiac paralysis with later, but sudden, onset, coming on, so to speak, in full health, and accompanied with considerable frequency of the pulse; (3) cardiac paralysis developing more slowly, when there already exist other paralytic phenomena; prognosis is less unfavorable. The symptoms of respiratory and cardiac paralyses may be united and give rise to bulbar crises, indicated by Duchenne under the name of "bulbar form of diphtheritic paralysis" The patient has crises of asphyxia, finally fatal, or he may be carried off by an attack of syncope.

The troubles of sensibility are very frequent in diphtheritic paralysis. Almost always they attack the paralyzed regions; often, however, we note akinesis without anæsthesia. The most frequent alteration of sensibility is anæsthesia; exceptionally there is hyperæsthesia, which is announced in the lower limbs by numbness and formication, and generally precedes the paralysis. Frequently the anæsthesia, when it exists, does not extend above the knees or elbows, but this localization is not constant, and the anæsthesia may

be generalized. It is sometimes accompanied with analgesia so complete that surgeons have been able to perform cutting operations without chloroform. The anæsthesia may affect the lips, tongue, and cheeks; and in rare cases the special senses of hearing, smell and taste have been abolished. The speech is often hesitating, stammering.

A capital fact in diphtheritic paralysis, one that distinguishes it from all other paralyses by peripheral neuritis, is that there is no muscular atrophy; the paralyzed limbs always retain their normal aspect and volume.

In very rare instances the velum pendulum is not affected, and the disease is localized in one muscular group without attacking other groups or other parts; such are the cases where the paralysis takes on the paraplegic or hemiplegic form, or where it is limited to the eye muscles, to a forearm, a leg, the hands, the feet, the lips, the anus, or the muscles of the trunk.

In the localized form the paralytic accidents may be essentially transient, and may disappear after a few days. In such cases the enfeeblement of the velum pendulum only manifests itself by a little dysphagia; now and then a little liquid flows back through the nose, but the patient on the whole swallows well. This is what happens also after tracheotomy; the drinks flow back by the cannula for a day or two.

The paralysis of the velum pendulum may last a

considerable time, but in general, when it remains limited, it is perilous only by the dangers of asphyxia to which it exposes the patient in the possible passage of aliments into the air-tubes. When the paralysis is generalized, its course is slow, lasting weeks or even months. Yet it is not rare to see the early paralysis disappear in a few days, to return during convalescence under a different form. Landouzy has described a form of diphtheritic paralysis whose course resembles that of the acute ascending paralysis of Landry, attacking successively the lower limbs, then the upper, as well as the muscles of the trunk, accompanied by bulbar accidents, and terminating rapidly in death without any trouble of sensibility. Some writers have regarded mobility and diffusion of the symptoms as characteristic of diphtheritic paralyses; but though these attacks do sometimes pass from one limb to another, then return to the one first affected, such alternations are not the rule. If frequently the paralysis invades successively the different vital apparatus in the order which we have adopted for the symptomatic description, there is nothing fixed about it. When one organ is affected, no one can foresee which member will suffer next; nothing gives assurance as to the time that the akinesis is to remain fixed to one part, for the paralytic phenomena sometimes present remissions and exacerbations which defy any prevision.

The paralysis terminates in recovery more than

eight times out of ten; in these cases, power of movement reappears first in the lower limbs, then in the throat, then in the upper members, the trunk, the viscera, the eye. Generally the organs paralyzed first are the first to recover. There is, however, no fixed rule even here, and it often enough happens that after having been the first affected, the velum pendulum is the last to resume its functions.

When the termination is fatal, death may take place slowly, rapidly, or suddenly. If slowly, the patient becomes cachectic and more and more feeble; the profound troubles from which he suffers are generally attributed to inanition, as he refuses to take food for fear of suffocation or of reflux by the nares. But it has been observed in these cases that feeding by the stomach-tube does not always suffice to save the patient. The cachexia, therefore, must be referred to the diphtheritic poison.

Writers have mentioned as occasionally occurring after diphtheria, nervous affections distinct from the diphtheritic paralysis: pseudo-membranous meningitis, of which three striking cases are on record; hemiplegia following cerebral hæmorrhage; multilocular sclerosis; attacks of mania, of symmetrical asphyxia of the extremities, of hysterical paralysis. Lyonnet even mentions certain arthropathies of nervous origin, a sort of trophic peri-articular affection supervening during convalescence from diphtheria.

COMPLICATIONS DUE TO SECONDARY INFECTIONS.

We have seen, in studying the secondary infections of diphtheria from a bacteriological point of view, that the streptococcus *pyogenes*, often found in the false membrane associated with the Loeffler bacillus, may invade the circulation and infect the entire organism. It thus produces a general septicæmia which much modifies the clinical aspect of the disease.

Gangrene may invade the points attacked by the diphtheria. The parts subjacent to the false membrane soften; the latter becomes black, and gives off a fetid odor. The gangrene may extend in surface and in depth, and hasten the fatal termination.

Suppurations are numerous, with multiple localizations; note the middle-ear otites, the glandular abscesses, the phlegmons of the neck, the perichondrites of the larynx, the suppurations of the trachea, etc. Cutaneous suppurations, patches of impetigo, pustules of eczema, multiple whitlows, boils, frequently accompany diphtheria in children.

Endocarditis is very rare; Sanné in 149 cases had not seen one with this complication.

I have placed among the secondary infections the diphtheritic erythemata, because in his recent work Mussy attributes to the streptococcus their production in most cases. These erythemata resemble

those met with in the false (streptococcus) diphtherias, and in puerperal fevers. (This pathogenic explanation demands further substantiation.)

The frequency of these erythemata is variable—once in thirty cases, sometimes once in four or five cases. Adults are much more subject to them than children. They are early, appearing during the first week; or they may be late, and testify to a profound infection of the organism, to be certainly followed by death in a short time. The eruption appears in certain favorite localities, about the wrists, elbows, knees, ankles, the upper part of the thighs; in general, it respects the face.

Robinson describes two species of erythema appearing in the course of diphtheria; the one early, transient, apyretic, scarlatiniform, without desquamation; the other tardy, special to toxic diphtheria, multiform, and rubeolic.

Mussy describes a multiform erythema, lasting from one to four days, neither desquamative nor pruriginous; a scarlatiniform non-desquamative erythema; a rubeolic erythema; and a purpuric erythema, associated or not with a multiform erythema. Fraenkel considers the latter one of the most frequent eruptions of diphtheria. This variety may appear at the onset or at the end of the disease. It is constituted by little hæmorrhagic spots whose size varies from that of a pea to that of the head of a fine pin. This eruption may easily pass unperceived.

Broncho-pneumonia may complicate all the localizations of diphtheria, but is met most frequently in the course of croup, and especially of croup after tracheotomy. It is more frequent in the infant under four years, and more grave in the adult. When it accompanies diphtheritic angina, it is generally because we have to do with a hypertoxic form of the disease; the broncho-pneumonia is then early. In croup we observe it sometimes from the first days before tracheotomy, sometimes two or three days after the operation, sometimes later still, when all danger seems to be over.

In the hypertoxic diphtherias, the physical and functional signs of the broncho-pneumonia remain completely masked, and the pulmonary lesion is only recognized at the autopsy. In the other forms of diphtheria it is easier to recognize. But it is always necessary in children to base a diagnosis rather on the general symptoms and functional disorders than on the physical signs, which are tardy and obscure.

In croup, if the broncho-pneumonia comes on after tracheotomy, the infant is pale and restless, the dyspnœa being very marked and characterized by a great frequency of the respiratory movements, with beating of the alæ nasi. This is apparent when the voice is not altogether extinct, when there is no attack of suffocation, and the stridulous inspiration is very little accentuated. The skin is burning hot, the temperature very high. Auscultation reveals nothing

characteristic. If, however, it is thought desirable to practice tracheotomy, the operation is not followed by any relief, and the infant dies at the end of a few hours.

When you perform tracheotomy, even though the broncho-pneumonia may not have already complicated the disease, you have still to fear lest the lung may be infected secondarily to the operation. If the respiration becomes noisy, and rises above forty or fifty per minute, if the expectoration becomes suppressed, and if the cannula becomes dry, so that the air produces in passing through it a peculiar whizzing sound, you may be sure of a broncho-pulmonary complication. At the same time the wound becomes grayish, and soon expectoration is reëstablished, and the cannula gives vent to a puriform sanies which blackens it. The temperature, which usually falls two or three days after the operation, remains about 40° C. The pulse is more than 150 per minute. Auscultation still gives very doubtful results. The blowing cannula-sound masks or modifies the pulmonary signs; you may, however, distinguish large mucous râles and sometimes a souffle.

When the broncho-pneumonia is tardy, it comes on at a period when the patient seems to be out of danger. The later its onset, as a rule, the more favorable the prognosis; it is always, however, a very grave complication, and kills nine times out of ten.

Erysipelas is a very rare complication in diph-

theria, apart from croup and tracheotomy. Sometimes it supervenes after the latter; you will then see the red, tumefied borders of the wound so characteristic of this complication. The lips of the tracheotomy wound then become dry, take on a palish-blue tint, and retract; the redness and swelling extend to the neck, face, and whole body. The general state now becomes worse, the temperature suddenly rises, and with the extension of the erysipelas the patient becomes restless, delirious, and irremediably comatose.

Measles sometimes complicates diphtheria, especially in children's hospitals, where it has such opportunities to spread. This exanthem is more likely to attend croup, and especially after tracheotomy. The invasion of the diphtheria is announced by an arrest in the cicatrization of the wound, and by high fever. From the first few days a broncho-pneumonia is present, which carries off two-thirds of the patients.

Scarlatina complicates diphtheria much more rarely than does measles. I saw it prevail as an epidemic in August, 1889, in a barrack hospital, among diphtheritic patients there quarantined, when it proved very fatal. The onset is announced by high fever, soon followed by the characteristic eruption.

Whooping-cough is a rare complication of croup. The paroxysms do not increase by the attacks of suffocation, but broncho-pneumonia soon sets in, with all its dangers.

CLINICAL FORMS.

We may, with Trousseau, admit three forms of diphtheria: the simple or benign, the infectious, and the form that is toxic at the start. This division corresponds sufficiently well with clinical observation.

1. *Benign* diphtheria generally appears under the form of sore throat, but sometimes attacks primarily the larynx, and we have then croup from the start. The disease announces itself by a slight fever, prostration, and malaise. When angina is the primary manifestation, there will be redness and swelling of the tonsils—often of only one. Over the swollen tonsils a white exudate forms, well circumscribed, semi-transparent, which rapidly thickens and thus constitutes a loosely adherent false membrane. Sometimes, instead of forming a patch covering a part of the tonsil, the membrane develops by lenticular points well separated, resembling herpes of the throat. An eruption of herpes on the lips may increase still more the difficulties of diagnosis. Glandular enlargement is the rule, but has, perhaps, less importance than Trousseau assigned to it. The false membrane remains localized to the throat except in rare cases, where it gains the larynx and constitutes a purely mechanical danger; but the disease remains benign, and, if it is possible to avoid asphyxia, recovery is not delayed.

These benign manifestations of diphtheria are of

short duration; recovery follows at the end of six or eight days. Albuminuria is generally lacking; paralysis sometimes appears, however, during convalescence. However slight the disease seems, and however inconspicuous the blood-poisoning, these benign forms are able to transmit grave diphtheria. This is the first argument to advance to those who are unwilling to recognize diphtheria in these light manifestations. The second argument is furnished by bacteriology, which has revealed the presence of the bacillus of Loeffler in all its virulence in these false membranes, so little inclined to invade the surrounding parts.

Furthermore, there exist abortive cases, in which the local symptoms are almost imperceptible, amounting only to a simple redness of the throat; the false membrane is insignificant or absent. Nevertheless these cases are met with in times of epidemics by the side of the malign forms; their origin is the same, and they may, in their turn, give rise to malignant diphtheria. We must also add that these abortive cases, with local manifestations almost *nil*, may in some cases develop general symptoms of extreme gravity.

2. *Infectious* diphtheria generally establishes its primary focus in the throat; it may, however, first appear on other mucous surfaces or even on the skin. The general condition may be the same at the onset as in the benign form, but as a rule the fever is quite high. The aspect is one of extreme depression. The counten-

ance has a pale, leaden hue; the mucous membranes are cyanosed. The intelligence is intact during the entire disease, but the general prostration is pronounced. What specially characterizes this form is the capital importance belonging to the local symptoms: the false membrane is essentially invasive; it spreads largely over the tonsils, the soft palate and uvula, gains the nasal fossæ, the larynx, the bronchi, the lips, the conjunctivæ, the genital organs, and covers the surface of blisters, wounds, and spots of impetigo. In the gravest cases it takes on a dark-grayish color with gangrenous appearance; the odor is fetid; the glandular swelling is very marked. In the less severe cases, there is always generalization of the false membranes, but without the gangrenous aspect; and the adenopathy is very moderate. Lastly, in certain cases, the disease for several days has the appearance of a benign diphtheria well localized; then suddenly it takes on an invading course, and spreads in less than twenty-four hours to the nasal fossæ, the larynx, and the bronchi. The albuminuria, more frequent than in the first form, is not constant; but the croup and the pulmonary complications are here the rule, and constitute all the gravity of the infectious form. Death is a frequent termination. During convalescence, diphtheritic paralysis frequently supervenes.

The progress is slow; the disease lasts generally from ten to twelve days, sometimes a month; in certain exceptional cases the patient continues to cough

out false membranes for several months (the chronic diphtheria of Barthez).

3. In the *toxic* form the danger is no longer confined to the localization of the false membrane and its rapid invading tendency; the exudation plays only an insignificant part compared with the profound and rapid intoxication of the organism.

The accidents may assume a fulminant form, with intense fever and rapid collapse, the production of false membranes being variable, but glandular engorgement excessive with infiltration of the neighboring cellular tissue; the patient in a few hours falls into a typhoid state, which terminates in death in the course of twenty-four to seventy-two hours.

But the disease generally lasts rather longer. The false membranes easily spread from the original focus in the throat, and take on a gangrenous aspect and fetid odor, the underlying mucosa bleeding at the least touch. Hæmorrhages are the rule—from the nose, mouth, anus, urethra, sometimes even from the stomach and bladder. Albuminuria is constant. The glands are extremely swollen. The pulse is rapid and becomes filiform; the extremities are cold; the temperature of the body is below the normal; the patient lies in a state of somnolence very like coma. Death is certain, and generally occurs before the end of the first week.

Sometimes the evolution of the toxic diphtheria is quite insidious; the false membranes are of little

extent, have no tendency to invade, and often disappear at the end of five or six days. But from the onset the glandular swelling is enormous, the pulse is wretched, the face livid; then as the local symptoms improve, the prostration augments, the pulse becomes feebler, the skin cold, and the patient succumbs.

In ambulatory toxic diphtherias the local lesions and the fever are without importance; the patient keeps up and is able to walk; but the paleness of the face and swelling of the neck cause the physician to be watchful from the onset. These diphtherias terminate unexpectedly in sudden death, or they may end in an unforeseen manner in the terminal accidents of the collapse.

Forms Differentiated by Bacteriology.—Loeffler's bacillus being recognized as the specific agent of diphtheria, it was but natural that efforts should be made to harmonize the different clinical aspects of the disease with the results yielded by bacteriological examination of the false membrane; in other words, to ascertain if the Loeffler bacillus suffices of itself to explain the entire symptomatic tableau of diphtheria, or if in some cases there is not warrant for attributing a part or the majority of the symptoms to associated pathogenic microbes. Grancher has attempted this division, and has proposed the name "toxic forms of diphtheria" for those cases in which the Loeffler bacillus is alone operative, as distinguished from the

"infectious form" in which the clinical picture is completely modified by the secondary infections.

From a symptomatic point of view, we shall see that these two forms are quite different from those which bear the same name in Trousseau's classification.

Barbier has attempted to justify the division proposed by Grancher, and has studied quite specially the influence of the streptococcus *pyogenes*, so often noticed in the false membrane, on the course of diphtheria. He admits, first, a *pure diphtheritic angina* (toxic angina of Grancher), due to the Loeffler bacillus and to it alone. These are the principal characters: sore throat often *nil* (this first phase of the disease may be latent and pass unperceived); there may be no fever, headache, or backache; the child is in not quite its usual good spirits, a little cross, and this is all; on examining the throat, typical white false-membranes, more or less easily lifted in flakes, are seen, but the mucosa is almost normal, neither red nor swollen; adenopathy absent or scarcely appreciable. Propagation to the larynx is frequent, and the symptoms of this may be the first to indicate the proper diagnosis. The future of these patients, if the type remains pure, is equally characteristic. It is in them that we witness the bronchial diphtheria, with expulsion by the cannula of pseudo-membranous casts, which latter often lead to fatal asphyxia. They have coryza, but it is diphtheritic in every aspect, with

closure of the nasal passages and obstructed mucous discharge. The false membrane, by hindering the entrance of air, determines the respiratory impediment or arrest by the nares. The cannula at no time gives vent to pus or muco-pus; it is dry. Death results from asphyxia pure and simple, or possibly from the nervous accidents—syncope, paralysis—or systemic intoxication. If recovery follows, the patients retain an anæmia more or less marked, and remain exposed to nervous accidents of paralytic nature during convalescence.

M. Barbier then considers the phenomena which belong to the association of the diphtheria bacillus with the streptococcus as shown by bacteriological examination. In these cases the streptococcus has been found, not only in the throat, but also in the viscera and in the blood, and all the complications were either certainly or probably of streptococcus origin. The following description shows how this microbian association manifests itself clinically, giving rise to the streptococcus form of diphtheria, one of the varieties of the "infectious form" of Grancher: "Typical external aspect of face and neck: Face pale, swollen or cyanosed, leaden hue; skin shiny and sometimes rosy red around the nose and on the nose itself; redness and excoriation of the upper lip beneath the nostrils; mouth open, breath horribly fetid when the bacteria of putrefaction have invaded the exudates, which is not rare; the act of swallowing is very

painful; the patient refuses nourishment; throat much tumefied, the mucous membrane red, sanious, bleeding, swollen; false membranes often dissociated and absent, or even thick and flabby, putrilaginous; neck enormously swollen, owing to the tumefaction of the glands, which are, as it were, buried in an œdematous infiltration of the cellular tissue of the neck; abundant nasal discharge, sero-fibrinous, sero-sanguineous, color of tobacco-juice, or even completely hæmorrhagic—so great is the abundance that sometimes the liquid flows by drops. The disease often kills in the course of twenty-four hours; if the patient lives longer, complications due to the streptococcus appear. The prostration of the patient, or oftener the extreme agitation, the high fever, sometimes convulsions at the end, are the principal general phenomena observed. Recovery is rare in the infectious forms; convalesence protracted. The throat, nose, and the outer border of the nose, long remain red and excoriated; grayish ulcerations, locally painful, are seen in the throat, and in certain cases actual losses of substance affecting the pillars of the fauces and the soft palate occur. Later complications, such as suppurative adenites, phlegmons, etc., may still retard the recovery and even produce death."

This attempt at classification of the clinical forms of diphtheria is interesting, though necessarily incomplete, and it indicates well the way to take in order to complete our knowledge of the characters so varied

and so dissimilar which diphtheria may present. There remains still to be studied the action on the economy of the micro-organisms of the false membranes other than the streptococcus, and to group together a great number of facts well studied in order to fix definitely these different aspects which the microbian associations impress upon diphtheria. Quite recently, Martin has reported cases which seem to show that the bacillus of diphtheria, associated with a coccus which often appears as a diplococcus capable of forming abundant colonies on serum, which bear a marked resemblance to those of the Loeffler bacillus, gives rise to a quite benign form of diphtheritic angina; while the association of the staphylococcus *albus* with the specific bacillus implies a prognosis much more grave.

DIPHTHERIA IN ADULTS.

Diphtheria is quite rare in adults; when it does occur, it is generally more grave than in children. Very benign epidemics among adults have, however, been reported. And in cases where the toxine of diphtheria spares the patient, respiratory complications of a grave, often fatal, character, are liable to supervene. The aspect of croup in the adult is different from what it is in the child; the glottis being large, the false membranes very seldom become sufficiently developed to completely occlude it and prevent the entrance of air. Moreover, the false membranes hardly ever remain limited to the laryngeal cavity; the laryngitis is accompanied by pseudo-membranous tracheo-bronchitis.

Croup in the adult has a progressive course; it does not pass through the three very distinct periods observed in this disease in children. The voice, which almost always escapes complete extinction, may remain normal till death, although the vocal cords are covered with false membranes. The dyspnœa is progressive, without attacks of intercurrent suffocation. Death by progressive asphyxia is the rule; it comes on tardily, on the average at the end of two or three weeks. The concomitant manifestations along the entire bronchial tree easily explain why tracheotomy is of so little relief to the adult. At the same time this operation should not be neglected

in cases of threatened asphyxia, for instances of cure due to tracheotomy are on record.

Very often in the adult, diphtheria takes the hypertoxic form. The patients are overwhelmed from the onset. The extremities are cold; the pulse small, irregular; the face pale, of a leaden hue; the breath fetid. A yellowish serosity flows by the nasal fossæ, of sickening odor. The patients are also enfeebled by an incessant diarrhœa. The throat is lined with thick, putrilaginous false-membranes, and when these are removed a bleeding surface is left behind. The blood mixes with the exudate and colors it; the mucous membrane itself takes on a darkish hue, as if gangrenous. The submaxillary glands are very much engorged and painful, the surrounding cellular tissue infiltrated, and the entire neck tumefied. If the air-passages are invaded, the symptoms of croup are scarcely apparent; the dyspnœa and the cough are so little marked as hardly to attract attention to the larynx. The patients die of the blood-poisoning rather than by asphyxia.

We know with certainty that the form of puerperal infection called diphtheritic, accompanied by false membranes on the vulva and vagina, is not due to the Loeffler bacillus. True diphtheria is very rare during pregnancy.

SECONDARY DIPHTHERIAS.

When diphtheria supervenes in the course of another disease, it generally takes on a very marked character of malignancy, and localizes itself especially on the organs which are attacked by the primary disease. Its course is rapid, especially when it leads to death. Diphtheria may complicate all diseases: tuberculosis, typhoid fever, pneumonia, etc. It is less often a complication of scarlet fever than has been supposed. It very exceptionally attends the onset of scarlatina, for the pseudo-membranous angina of this period is seldom of diphtheritic nature. On the other hand, the pseudo-membranous anginas which supervene at a late period (the second week) are almost always manifestations of diphtheria; the scarlatina, after a normal course of a few days, has disappeared, as well as the initial angina, the temperature has fallen to the normal, desquamation has already set in, when unexpectedly the general condition becomes aggravated, the child grows pale, the fever kindles up, and the glands of the neck become engorged. On examining the throat, we find it filled with grayish false-membranes. Patients affected with these late anginas generally succumb rapidly with all the symptoms of diphtheritic poisoning.

Diphtheria following measles is also of extreme gravity. Under two years, death is almost certain; patients die of infection or of broncho-pneumonia.

Diphtheria is very rarely a complication of whooping-cough, appearing chiefly during the spasmodic period. The paroxysms of coughing may then act favorably in aiding the expulsion of the false membranes. According to Vaquer, the toxic form is rarely observed, but broncho-pneumonia is always to be dreaded. It will not do to hesitate to practice tracheotomy when indicated, for this operation has saved a number of lives.

Diphtheria secondary to typhoid fever and small-pox terminates fatally in a few days. As a complication of typhoid fever it rarely assumes a form other than the hypertoxic.

PROGRESS—DURATION—TERMINATION.

When studying the clinical forms of diphtheria, we saw that this disease was complex, and that it would be impossible to include a satisfactory account of its course in one description.

In one case, for example, diphtheria appears in a benign form, remains local and circumscribed, occasions a little fever for a few days; the false membranes hardly re-form, soon disappear, leaving a little redness of the mucosa. All the symptoms disappear in about a week; the patient, however, remains for some time pale and feeble, and has a slow convalescence.

Again, the production of the false membrane is exuberant and becomes a real danger. It spreads rapidly, invades new surfaces, and when removed is reproduced; the general condition is not bad, but the exudation may at any moment obstruct the air-passages, and then asphyxia is imminent. This form sometimes lasts a fortnight, sometimes a month.

Take another case: The patient is unconscious, his countenance livid, neck and face much swollen, respiration panting and becoming extinct. Profound systemic intoxication is present. It often requires an attentive examination to find the false membrane which is the origin of all the evil. In the course of five or six days, sometimes in twenty-four hours, the diphtheria has invaded the entire organism.

By these examples it is apparent how variable is

the course of the disease. At the same time, when the false membrane does not remain absolutely localized at the point of primary infection, the process of invasion follows a sufficiently regular course: you see the membrane spread to the throat, nasal fossæ, larynx, trachea, bronchi, etc. If the law of Bretonneau and of Trousseau, thus formulated: "The propagation takes place in an invariable order from the upper parts to the lower"—if this law is not absolute, it nevertheless indicates how completely these two observers had recognized a sort of *auto-inoculation*, of successive contamination of the parts below by a liquid secreted by the false membrane above. Evidently the contagion may spread upward as well as downward, as in cases where it passes from the pharynx to the Eustachian tube, and from the nose into the nasal duct; but we must not forget that there are also instances where the contagion is carried by the fingers of the patient or those of his attendant. But these facts are not sufficient to invalidate the law of Bretonneau, which finds justification in practice. Diphtheria usually runs its course in from two or three days to a month. There are exceptional cases where the diphtheria becomes chronic and the patient continues to expel false membranes after two or three months.

Death is the termination of diphtheria in more than two-thirds of the cases; it may supervene suddenly during the first two or three days of the disease.

Sometimes it terminates the hypertoxic anginas with fulminant development, the patient succumbing to a veritable hyperacute septicæmia. Then again, in diphtheria which has early invaded the air-passages, in a few days menacing asphyxiating symptoms appear; this is the *strangulatory* diphtheria, against which tracheotomy remains powerless if there be pseudo-membranous bronchitis, or if the diphtheria be complicated with broncho-pneumonia. Sometimes the patient succumbs to the early cardiac paralysis first mentioned by Henoch.

During the stationary period (fastigium), croup and broncho-pneumonia are likely to carry off the patient more or less rapidly. When there are no diphtheritic manifestations in the air-passages, the disease may terminate slowly by a progressive cachexia, due either to the nature of the intoxication or to the disorders produced by secondary infections, such as gangrene, phlegmons of the neck and groin, mediastinitis, erysipelas, or an intercurrent eruptive fever.

Even in convalescence, all danger is not past; an acute myocarditis, passing from latency to activity, may cause sudden death. Rapid asphyxia is always imminent when the respiratory muscles become paralyzed; this frequently happens as a sequel in diphtheritic paralysis. Sudden syncope follows a crisis of bulbar or cardiac paralysis. In full convalescence, broncho-pneumonia may attack a patient and carry him off.

Recovery very often follows the simple forms of diphtheria. Unfortunately these are far from being most frequent. Not all patients succumb to those invasive diphtherias which constitute the "infectious form" of Trousseau; some of them will resist croup, tracheotomy, broncho-pneumonia, the paralysis of convalescence. But the toxic or hypertoxic form is always fatal.

Recovery is announced by the progressive disappearance of the false membranes, which reappear more and more slowly; the adenopathies diminish, the general state improves, and after a convalescence always rather slow, complete restoration comes about.

A first attack confers no immunity from future attacks; the patient is subject to relapses and recurrences. It is not rare to see the false membranes reappear several days after the advent of convalescence. There is nothing surprising about this, for we know that the bacillus with all its virulence lives in the mouth for some time after the false membranes have completely disappeared. I have seen croup follow recovery from a benign diphtheritic angina. Often the second attack of diphtheria is more benign than the first, but there are numerous exceptions to this rule.

Relapses may be occasioned by eruptive fevers, such as measles or scarlet fever. Single recurrences of diphtheria have been frequently noted, and in some cases even multiple recurrences.

PROGNOSIS.

When the false membrane remains localized and shows little tendency to spread and to be reproduced, the air-passages remaining free and the neighboring glands being little affected, the general state good, and little or no albuminuria, there is reason to regard the disease as benign and to hope for a favorable termination. But the diphtheria none the less remains a grave disease, for even in these cases, so ight in appearance, there is always danger of late croup, a myocarditis, or a paralysis during convalescence.

Diphtheria comprehends three factors of gravity: the patient, the disease, and the environment.

Diphtheria is particularly grave in the infant and in the adult. Before the third year of life it is almost always fatal.

The previous health of the patient is also a matter of importance. Lymphatic or scrofulous subjects appear to present a favorable soil for grave infections. The malignancy of secondary diphtherias we have already discussed.

The course of the disease may be influenced in a capital manner by the degree of localization of the diphtheritic infection, by the extent of systemic intoxication, and by the nature of the infectious complications.

The rapid extension of the false membranes to

the nasal fossæ, the larynx, and the bronchi, is of special gravity by reason of the mechanical troubles it occasions. As for the pseudo-membranous coryza, it is always of bad prognosis, for it indicates the intensity of the infection. Often the quite special virulence of the bacillus is already announced locally by the putrilaginous, sometimes gangrenous, appearance of the false membranes.

The poison soon makes its action felt on the entire organism. The glandular engorgement, the pallor of the visage, the prostration, the hæmorrhages of the first few days, especially that constant oozing from the mouth and throat which we so much dread to see, are precious elements of prognosis; the fever and albuminuria are much less important.

But the intoxication may be slow and insidious, suddenly manifesting itself in convalescence by a myocarditis or paralysis. It is at the advent of convalescence that it is necessary particularly to watch the heart, whose most profound lesions announce themselves only by troubles trifling in appearance—a little præcordial distress, palpitations, lipothymia. Likewise, a paralysis which begins by an insignificant difficulty of deglutition may become rapidly general and carry off the patient in a few days.

Secondary infections may determine veritable septicæmias, at the same time that they aggravate the virulence of the diphtheria bacillus; the extreme pallor of the countenance, the deformation of the in-

filtrated neck, the yellowish, sanious and fetid discharge from the nares, the agitation or the somnolence, the general enfeeblement, leave no doubt as to the issue of the disease.

The gangrene which may complicate the diphtheria testifies less to the dilapidation of the patient's organism than to the gravity of the disease itself. It is nevertheless of serious prognosis.

There is general agreement that the infectious erythemata which supervene at the onset of diphtheria have no influence on the course of the disease. It is not so with the late erythematous rashes, which are almost always precursors of death.

Broncho-pneumonia is one of the most grave complications of diphtheria. We have seen how little we can depend upon the physical signs in making a diagnosis. It is chiefly the coincidence of a very high elevation of temperature with a marked and growing dyspnœa that will help the practitioner to recognize this affection, which is so very fatal.

Bad hygienic conditions, close, ill ventilated rooms, overcrowding, want of cleanliness or of nourishment, are unfavorable circumstances.

The danger is of course greater in certain epidemics of peculiar malignancy; diphtheria is also especially fatal in large cities. It is generally very malignant in winter and in the spring time, in cold and damp seasons, and in certain northern countries such as Sweden, Norway, Denmark, and Northern Germany.

DIAGNOSIS.

The elements which contribute to the diagnosis of diphtheria are not all of equal importance. The principal one, undoubtedly, is the false membrane—a fibrinous exudation, of whitish or grayish color, quite adherent to the parts beneath, forming when removed a coherent lamina insoluble in water, and reproduced in the throat after ablation. Angina being the most frequent manifestation of diphtheria, the presence of a pseudo-membranous exudation on the tonsils is very significant, especially when it spreads to the soft palate and the uvula.

The engorgement of the glands corresponding to the region invaded by the false membrane, the pallor, the general enfeeblement of the patient, the albuminuria, may also give valuable indications. The paralysis during convalescence, even, by its special behavior and evolution, is enough sometimes to warrant a retrospective diagnosis when every other manifestation of the diphtheria has disappeared.

But these characteristic symptoms are not always very apparent. In very young children, particularly, the disease is frequently overlooked by reason of inattention to the throat. Trousseau with good reason advises to examine the throat in every case of ill-defined infantile sickness.

Every one of the elements of diagnosis above mentioned may be wanting. Anginas without false

membranes have been observed in the course of certain epidemics. They alternate with the pseudo-membranous manifestations, are contracted by contact with an undoubted case of diphtheria, and transmit an angina with characteristic exudation. But these "diphtherias without diphtheria" are too exceptional to occupy us long. On the other hand, it is not rare to see the false membrane appear discrete and become detached in a day's time or less, and not again be reproduced; nor need the ephemeral nature of the characteristic local symptoms have any influence on the evolution of the disease. In other cases, and especially in he benign forms, the glandular engorgement is wanting; the general condition may remain good; the albuminuria may be absent. An eruption of herpes on the lips or nares is not a symptom of much significance, for it may coincide with genuine diphtheria as well as with herpetic angina.

The diagnosis of acute diphtheritic myocarditis is very difficult. In the young child who in full convalescence is suddenly carried off by a syncope, the cause of the terminal accident is very difficult to determine and to distinguish from a cardiac paralysis, if the medical attendant has not previously noted an extreme feebleness of the pulse accompanied by cardiac intermittences. In the adult the symptoms evolve less rapidly; first a præcordial anguish, then cardiac excitation, soon followed by feebleness of the organ with irregularity and softness of the pulse,

dyspnœa, collapse, and repeated syncope. Unhappily, these symptoms may accompany pleuro-pneumonia or pericardiac complications, which must first be eliminated by an attentive examination before the physician can decide that he has an acute myocarditis to deal with.

The diphtheritic paralysis is generally easy to recognize, especially when account has been taken of the manifestations of diphtheria which have preceded it. In the exceptional cases, where the paralysis remains localized to the lower members without having ever affected any other part, it is distinguished from certain peripheral neuritic paralyses, and particularly from alcoholic paraplegia, by the absence of pain and especially of muscular atrophy. If it sometimes has a superficial resemblance to general paralysis, glosso-labio-laryngeal paralysis, multilocular sclerosis, or locomotor ataxia, it is sufficient to bear in mind its history and peculiar signs in order to avoid any confusion.

We have already seen of how little help are the physical signs in enabling one to decide as to the invasion of broncho-pneumonia in the course of diphtheria. A high fever, a marked and continuous dyspnœa, with beating of the alæ nasi, even when there are little or no paroxysms of suffocation or of wheezing, are symptoms quite as precious as those furnished by auscultation and percussion.

Thrush rarely resembles diphtheria. It may,

however, extend to the throat, and even localize itself there exclusively, so as to cause doubt in the mind of the attending physician. The constitution of its grumous coating should dissipate these doubts. Moreover, if you take a little of the thrush membrane, crush it on a glass slide, and treat it with potassa, you will see under the microscope the mycelium and spores of *Oidium albicans*.

When diphtheria passes from the throat to the larynx, one is warned of the laryngeal nature of the lesion by noting the patches in the throat. But in cases of primitive croup or where the patches in the throat have disappeared, the diphtheria reveals itself only by the mechanical obstacle which it opposes to the respiratory functions. Now in the infant the affections which cause similar symptoms are numerous, by reason of the small diameter of the glottis. There is only one sign pathognomonic of diphtheria exclusively localized in the larynx, namely, the expectoration of a false membrane, and this is often wanting.

In laryngismus stridulus, the first access of suffocation comes on suddenly in the night; the patient may have had only a little cold in the head or a little hoarseness during the day, perhaps no abnormal symptoms whatever. In the interval of the paroxysms the voice is rarely altered, and the cough is resonant, the respiration calm; while in croup the voice and the cough are rapidly and completely extinguished, the

dyspnœa becoming more intense as the paroxysms are repeated, and never presenting complete remission.

Retro-pharyngeal abscess or œdema of the glottis may also narrow the glottic orifice so as to give rise to symptoms of asphyxia very like those of croup. It will not do to neglect exploration of the pharynx and upper part of the larynx with the finger introduced into the throat, before pronouncing on the nature of the disease.

The differentiation of the false diphtherias will be considered on the next page.

FALSE DIPHTHERIAS.

The affections just enumerated resemble diphtheria more or less, but it is almost always possible to differentiate them objectively. It is not so with the diseases we are about to study; they reproduce completely the clinical picture of diphtheria, and differ only by their course and prognosis. Often a bacteriological examination is absolutely necessary, to remove doubts. In a scarlatinous patient who in the first two or three days of the disease has had an erythematous angina, possibly accompanied by a pultaceous deposit, the aspect of the throat will be modified on the second or third day of the eruption, and thick lenticular points are visible at the orifice of the tonsillar crypts; these points soon run together and form a creamy coat with a pultaceous aspect, but with little power of resistance. The next day there is a firm, coherent false-membrane, which may be removed in large flakes. This pseudo-membrane invades the uvula and soft palate, and may spread to the pharynx. Very white at first, it soon becomes grayish or yellowish; may be strewn with black patches, the result of little hæmorrhages. The pseudo-membranous deposit is very adherent to the mucosa, and reproduces itself after ablation. Often, when it is removed, the mucous membrane underneath bleeds and shows an eroded, ragged, sloughy, indented surface. The dysphagia and sniffling are pronounced. There is accom-

panying this bad condition of the throat, engorgement of the submaxillary glands. The temperature is high.

According to the degree of extension of the false membranes, the gravity of the general symptoms, and the amount of general infection attributable to the angina, we may distinguish three forms of this sore throat: In the *benign form* the false membranes are very limited and have but little tendency to spread; the neighboring glands are only slightly swollen; the general condition is good, and the fever lasts but a short time; no complication sets in as a consequence of the angina; the false membranes may early invade the tonsils and uvula, but have little tendency to re-form, and rapidly disappear; the angina causes no general symptoms.—The *grave form* is characterized not only by the rapid extension of the false membranes, by their persistence, and by the intensity of the submaxillary engorgement, but also by the long duration of the angina, which, in the cases which I have observed, has lasted from nine to twenty-three days; the fever and general symptoms are prolonged, and there are almost always complications, such as broncho-pneumonia, nephritis, rheumatism, otitis, impetigo, etc.; this form does not of itself cause death, but it makes the prognosis doubtful by the complications which it entails.—If in the forms before mentioned, the symptoms independent of the angina are the most noteworthy, it is not so in the *scarlatinal septic form;* an atypical, fugacious eruption, scarcely

visible, characterizes this variety; the other symptoms depend only on the angina, which seems of itself to constitute the whole malady, hence the name of *scarlatina anginosa* which is often given it. The most complete descriptions of hypertoxic diphtheritic angina give a faithful portraiture of the septic angina of scarlet fever.

I have proved the existence of these different forms by numerous bacteriological examinations. By the process of sowing in striæ on gelatinized serum and gelose, I have made bacteriological examination of nineteen cases of pseudo-membranous angina at the onset of scarlatina. Only one of these anginas was of diphtheritic nature; in the eighteen other cases not a single colony of the Loeffler bacillus could be found, but the presence of the streptococcus *pyogenes* was constant in the false membrane.

It is to-day settled that pseudo-membranous angina at the onset of scarlet fever is almost never of diphtheritic nature; this affirmation is based on forty-five cases in which bacteriological examination was made with all the rigor possible. On the other hand, the pseudo-membranous angina which comes on at a late date in scarlet fever is almost always true diphtheria. In five out of six cases examined by Loeffler, Morel, and myself, the Loeffler bacillus was found, the sixth case being a streptococcus diphtheria, in which the patches did not appear till the twenty-seventh day, during convalescence.

We know there is a form of puerperal infection improperly denominated "puerperal diphtheria," in which true fibrinous false-membranes are found on the vulva, vagina, mucosa of the uterus and tubes, and even on the serous membranes. Suppurations are often among the symptoms. This fibrinous exudation presents characters very similar to those of diphtheritic membranes; but M. Widal has sufficiently differentiated them by showing that while the patches of diphtheria are due to the Loeffler bacillus, those of puerperal infection are the product of the streptococcus *pyogenes*.

It is not rare to note in syphilitic patients, sometimes on the surface of an infectant chancre, oftener on secondary syphilides, a thick, grayish, adherent false-membrane very like the diphtheritic exudate. When it forms only a simple grayish film, we have the opaline papule; when thicker, lamelliform, opaque, of a dull white color, it is the porcelain-papule of Fournier. It is in general on the genital organs of the female that we observe syphilitic lesions thus covered with false membranes; they may also be met in the throat, and strikingly resemble diphtheritic angina, for which they have been frequently mistaken. The onset of these diphtheroid anginas of syphilis is accompanied with engorgement of the submaxillary glands and with general symptoms often very marked: malaise, chills, cephalalgia, fever, pale and earthy hue of countenance.

The clinical signs which enable us to differentiate the pseudo-membranous syphilides from diphtheria are not constant. The objective characters of the false membranes are the same in both affections. At the same time, in most cases the diphtheritic patch may readily be detached with a swab, while the syphilitic exudate resists a mere rub. The subjacent mucosa is almost always intact in diphtheria; whereas it bleeds easily and almost always presents ulcerations when the false membrane is syphilitic. When true diphtheria spreads, it easily reaches the posterior pharynx and trachea; the diphtheroid syphilide generally respects the larynx, and does not spread beyond the anterior pillars of the soft palate. In syphilis, false membranes may be present on the hard palate, while this localization is exceptional in diphtheria. The pallor, the general prostration, the presence of albumen in the urine, are symptoms which pertain rather to diphtheria than to syphilis. The recognition of syphilitic antecedents, and especially the detection of concomitant secondary syphilides, plead in favor of syphilis. So much for the differential diagnosis of these two pseudo-membranous affections.

Roux and Yersin have noted several cases of primary pseudo-membranous angina which were not of diphtheritic nature. Menetrier reports a case in which he isolated the pneumococcus. Netter has also noticed the presence of the pneumococcus in

laryngeal false-membranes when there was no Loeffler bacillus present. In two cases which I personally studied in 1890, and which were tabulated as false diphtheria, both occurring in our hospitals, the pseudo-membranes did not contain the Loeffler bacillus, but gave fine cultures of the streptococcus *pyogenes*. Netter has also noted a case of diphtheroid angina due to streptococci and staphylococci. Baginsky, out of ninety-three cases of apparent diphtheria, found sixty-eight due to the Loeffler bacillus, and fifteen to staphylococci and streptococci. Examples of these false diphtherias have been given by Morel, Mussy, and Martin.

If most of these cases behave clinically like benign diphtheria, sometimes these false diphtherias are accompanied by grave general symptoms, such as infectious erythema, and great engorgement of the glands, and end in death.

PATHOLOGICAL ANATOMY.

We have to study successively the lesions provoked by the diphtheritic bacillus, those which are due to the action of the toxine produced by the bacillus, and those which result from the secondary infections supervening in the course of the diphtheria.

1. Lesions Due to the Diphtheria Bacillus.—We have seen that the diphtheria bacillus produces but one lesion, the false membrane. We have already studied the physical characters and the various localizations of the false membranes in the regions accessible to view. When at the autopsy we inspect the false membranes which have invaded the air-passages —larynx, trachea, and bronchi—we see that they have taken the form of these organs; they line them continuously or in patches. We meet them principally at the base of the epiglottis, on the arytenoepiglottidean ligaments, on the upper surface of the vocal cords, etc. In the trachea, they line chiefly the posterior wall. They may also be found in the sinuses of the face, the Eustachian tube, and the middle ear, to the walls of which they are moulded. It is very rare to observe them in the digestive tube. In the œsophagus they become elongated into bands lining the organ to some depth, or into cylinders more or less elongated. In the stomach they form very thin patches or rings around the cardia or pylorus. In the intestine they spread out in patches or form cylindrical moulds of the gut.

From a chemical point of view, a false membrane is composed of the following elements: fibrin, an amorphous substance, mucin, and fatty matters. A more interesting study because of its practical consequences is that of the action of chemical agents on the exudation. Very few acids have more than a slight action upon it; the mineral acids and acetic acid cannot dissolve it; it is, however, soluble in citric and especially in lactic acid. False membrane left in a 5-per-cent. solution of lactic acid dissolves in a few minutes. The same result takes place with the alkalies, potassa, soda, and lime. Lime-water has as rapid an action as lactic acid; and we may obtain still better results with a solution of caustic soda in glycerin.

Bretonnean was the first to establish the fibrinous nature of the false membrane, and to show that it is not constituted by an eschar of the subjacent mucosa. Since then, pathologists have explained the formation and constitution of the diphtheritic membrane in two ways: some hold that it is a fibrinous exudation, others that it is a special transformation of the epithelium of the mucosa.

The first view is supported by the French school —by Bretonneau, Trousseau, Laboulbéne, Robin— who regard the pseudo-membrane as an exudation of fibrin which in its coagulation imprisons epithelial elements, fatty matters, and various products of inflammation. The second theory is that of the Ger-

man school, first stated by Virchow, and subsequently developed by Wagner. The latter describes the formation of the false membranes in the pharynx by a process beginning with the development of a clear, homogeneous reticulum, the meshes of which contain lymphoid cells; this reticulum being directly derived from a particular metamorphosis of the pavement epithelia. The latter swell; little, clear, round-oval spaces develop around the nucleus, and increase in size while deforming the cell. At the same time the protoplasm resists further destructive agencies, and resembles fibrin by its chemical composition, while its nucleus disappears. The deformation of the cellular protoplasm becomes more and more marked; it elongates and forms filaments, which ramify in every direction, and, joining those which issue from neighboring cells, form with them a continuous network. The most superficial cells of the epithelial layer do not participate in these alterations. Below the glottis and in the trachea the exudation has still an epithelial origin, but as the epithelium is cylindrical the reticulum is closer. Wagner admits that this transformation of the cylindrical cells is much more difficult to see.

According to Leloir, we are to seek for a true conception in a sort of eclecticism—the epithelial alteration constituting, as he believes, a stage of onset, the fibrinous exudation corresponding to a more advanced stage. During the catarrhal period

of the diphtheritic angina, when there is still only redness of the tonsils, the epithelium swells, then its cells are glued together, and the false membrane is formed at the expense of a transformation and deformation of the epithelium different from that described by Wagner, but ending in the same result, an epithelial reticulum. Thus there is formed a network containing in its meshes leucocytes and fibrin in a filamentous state. If the duration of the false membrane is ephemeral, and if recovery is rapid, the process is arrested here; there is a complete disintegration of the exudation, which disappears, and a new epithelium is formed on the surface of the mucosa. If the disease continues, the epithelial reticulum undergoes disintegration, and to replace it the derm throws out fibrin and leucocytes which coagulate into a fibrino-purulent membrane. Little by little the metamorphosis goes on until there remain in the false membrane only a few granulo-fatty epithelial cells, and it is constituted throughout its extent by a fibrinous network containing leucocytes and a few red blood-corpuscles.

In the laryngo-bronchial false-membranes, vacuoles indeed form in the disaggregated epithelial cells, but there develops rapidly a fibrinous exudate which sometimes traverses the dissociated epithelium to constitute on its surface a more or less thickened muco-purulent fibrinous false-membrane; sometimes it raises the epithelium and forms under it a fibrino-purulent layer.

Leloir shows that there is no difference, macroscopic or microscopic, between the false membrane of diphtheria and that which is produced by experimentally irritating the pharyngeal mucosa, or which develops in herpetic angina, on mucous patches, indurated chancres, blisters, etc. In fact, the false membrane is only a pustule or a mass of confluent pustules, of which the centre is bare by reason of the absence of the horny layer.

Cornil has also studied the false membrane in diphtheria. He admits that the exudate is formed at first of a stroma of epithelial cells and leucocytes, then becomes entirely fibrinous. There is first a degeneration of the investing epithelium; then this is lifted up and detached by the migratory cells, which, by reason of the inflammation, issue in great abundance from the vessels of the mucosa. Later, when this epithelium is destroyed and does not form again, the false membrane is constituted only of a reticulum of fibrin and of leucocytes.

To sum up: It is admitted that the false membrane, wherever located, is always essentially the same. The importance of the epithelium in the formation has been much exaggerated; we indeed find pavement epithelium, especially at the outset, in the pharyngeal exudate, but fibrin is the principal element of the false membrane.

The Loeffler bacillus in contact with a mucous membrane produces an inflammation, which manifests

itself by the transudation of fibrin through the vessels, and by diapedesis of leucocytes. While the false membranes experimentally produced—by means of ammonia, for instance—are not, after removal, reproduced in the throat, the exudate of diphtheria is renewed as long as the cause that has produced it (the specific bacillus) remains present and preserves its virulence. These successive exudations may give a stratified aspect to the false membrane.

The false membrane may disappear in two ways: either it undergoes disaggregation, or it falls off. In the first case the fibrin loses its fibrillary character, becomes granular, may be transformed into mucin, softens, becomes diffluent, separates in fragments, and disappears. This process is accompanied by a notable diminution or even complete disappearance of the specific bacilli in the exudate, which is invaded by a host of other microbes; these bacteria probably contribute thus to alter the constitution of the false membrane.

The pseudo-membrane may become detached from the mucosa when the inflammation diminishes and the diapedesis and transudation of fibrin cease. The mucosa, on becoming normal, secretes mucus, which, insinuating itself between the surface of the mucosa and the exudate, breaks the filamentous adhesions which join the two, and detaches little by little the false membrane, allowing it to fall off.

2. Lesions Produced by the Diphtheritic

Poison.—Bretonneau, in endeavoring to demonstrate that the false membrane is not an eschar, affirmed the absolute integrity of the subjacent mucosa in all cases. He went too far; the mucosa is not unaffected. In the most simple cases it is congested but remains smooth; at other times, the inflammation being more intense, the mucosa becomes rough and loses its polish. Below the false membrane and in the zone that surrounds it, the chorion is infiltrated to such an extent as sometimes to give rise to œdema of the glottis; the mucosa is spotted with ecchymoses. Often, then, the region invaded is the seat of ulcerations more or less deep. Lastly, in certain malignant forms the mucosa takes on a violaceous tint, the diseased points become the seat of a considerable tumefaction, and a more or less extensive eschar forms which leaves after it a grayish ulceration secreting a fetid sanies. Roux and Yersin, in cases of experimental diphtheria (with the Loeffler bacillus alone), have observed destructive lesions of the affected region; these eschars at the point of inoculation have been reproduced by the injection of filtered diphtheritic culture-broths.

The action of the poison then suffices to determine vascular thromboses, which entail either fragmentary destruction of the tissues or a more extensive mortification. Then the microbes of putrefaction set up a true gangrene.

The histological lesions of the mucosa subjacent

to the false membranes have been studied chiefly in the throat and air-passages.

In the diphtheritic amygdalites, the false membrane is applied to the chorion of the mucosa completely denuded of its epithelium. We find on the points of the tonsils where the false membrane is absent or detached, an epithelium sometimes normal, sometimes constituted of one or two layers of cubical cells irregularly cylindrical or even vesicular, showing a cavity between the protoplasm and the nucleus. The chorion is infiltrated with lymph-cells and red globules. The capillary vessels are filled with white globules; the follicles and reticulated tissue of the tonsils are inflamed, stuffed with lymph-cells. When there is loss of substance of the mucosa, we find along with infiltration of the chorion a softening and separation of the connective-tissue fibres by fatty granulations, as well as the presence of little hæmorrhagic foci here and there.

In cutaneous diphtheria, the horny layer has disappeared, and the derm subjacent to the false membrane is thickened, red, indurated, and uneven; the subcutaneous cellular tissue is infiltrated and tumefied so that the borders of the ulceration are very salient and violaceous. The rete mucosum and superficial layer of the derm react precisely as the epithelium and chorion of the mucous membranes, as seen by the microscope.

All the glands are subject to engorgement, espe-

cially the submaxillary and parotids. At the autopsy, the bronchial and even the mesenteric glands are found hypertrophied. The engorged glands may fuse together and form a coherent mass, which by its size may cause compression symptoms. The cellular tissue around the affected glands is infiltrated, and the entire region deformed, tense, and hard.

Section of these glands presents the red or reddish-brown color of intense inflammation. The hypertrophied follicles appear as opaque, white, brilliant granules. Centres of necrobiosis have been described. Morel refers these lesions to the irritation of streptococci in the gland-parenchyma, these microbes being always present. The necrobiosis would, then, be the result of a secondary infection. He thinks that the diphtheria poison causes hypertrophy of the follicles, manifesting itself by a considerable accumulation of leucocytes which stain vividly. The blood-vessels are dilated and contain numerous leucocytes; but the stroma, the sinuses, and the capsule of the gland present no alteration.

In cases where the lesion depends only on the action of the diphtheritic poison, no micro-organism is seen in the sections.

The submaxillary and parotid glands present a considerable augmentation of volume, have a yellowish hue, and seem to be the seat of an œdematous infiltration. The histological examination shows profound lesion of their elements. The connective tissue

which surrounds the gland and its lobules has proliferated. The epithelium of the acini is first simply swollen and translucid, then it becomes granular and contracts; it may finally so multiply as to obstruct the gland cavities by cells of new formation. In many points the lobular ducts and acini are surrounded by little miliary abscesses. The production of pus in these cases must depend on secondary infections.

Generally voluminous, the liver presents the external aspect of congestion; it is deep red in patients who have succumbed at the onset of diphtheria. In cases that have lasted longer it is pale, often mottled with yellowish-white patches, indicating fatty accumulation. On section, no liquid is seen to ooze except in the early stage of congestion, when a little dark, thick, sanious fluid escapes. The microscope shows dilated capillaries and fatty infiltration of their endothelial cells and of the hepatic cells. It is a true infiltration and not a degeneration of the hepatic cells, for the latter remain living—their protoplasm is not modified, their nuclei continue to stain well; at the same time, in some cases their volume is notably diminished. The fatty accumulation may be periportal; it may be around the hepatic veins or occupy the entire extent of the lobule. Masses of embryonic cells may accumulate in the connective tissue of the portal spaces, forming nodules. The vessels contain a great many leucocytes. In short, the lesions are nearly the same as those met with in the liver in the course of all infectious diseases.

Degenerative lesions of the gastric mucous membrane are common in diphtheria affecting the stomach —the epithelium disappearing, subepithelial necrosis may follow. The intestine often shows traces of catarrhal enteritis, with tumefaction of its follicles and glands.

The spleen is congested and hypertrophied, the Malpighian corpuscles white and brilliant; the microscope shows an enormous accumulation of round cells around these corpuscles.

The lesions of the kidney are those of congestion or of parenchymatous nephritis, in general little pronounced. These lesions are often not symmetrical. When there is simply congestion, the kidney is augmented in volume, of reddish color, its external surface strewn with deep-red points (Verheyen's stars). On section, the congestion is found to be limited to the cortical substance, while the medullary substance remains pale.—When there is nephritis, the kidney is yellow, soft, mottled with spots of a clearer yellow; the cortical substance seems augmented in volume, is pale on section, and trenches by its prolongations on the medullary substance, which is very red; the capsule of the kidney is healthy, easily detachable without tearing the parenchyma. Under the microscope the principal lesions, when but little advanced, are seen to be dilatation of the blood-vessels and some cloudy swelling of the epithelium of the convoluted and collecting tubes—these alterations are

similar to those produced by phosphorus or arsenic, especially the latter; the glomerule is simply congested, its vessels distended and full of globules; there is rarely any exudation between the capsule and capillary tufts. In a more advanced stage, the epithelium of Bowman's capsules is in places degenerated and desquamated, in other places undergoing proliferation; there is a serous exudation, with blood-globules and epithelial débris in the cavity of the capsule; in the straight and collecting tubes the epithelium contains numerous fine fat globules; there are little hæmorrhagic foci under the capsule, and a granular detritus in the large convoluted tubes.

All these alterations seem due to the intoxication, and not to any secondary infection, for all who have sought for microbes in a diphtheritic kidney have failed to find any.

The heart is generally increased in size. If in many cases pathologists have noted the flabby consistence and dead-leaf color of the organ when spread out on the post-mortem table, it is not rare to observe under the microscope the lesions of acute myocarditis in a diphtheritic patient whose cardiac tissue remains firm, red, and of normal aspect. The heart is dilated, but not hypertrophied. Its weight is little if at all increased. Generally its cavities and large vessels are full of clots, which are either soft, like currant jelly (especially in the right cavities), or half fibrinous, half cruoric, prolonged into the blood-vessels. When

the heart cavities are emptied of their clots, you will often see under the endocardium ecchymotic spots, and the same may be observed, though rarely, upon the pericardium. There is a general or limited redness at the free border of the valves, and mammillated prominences forming a crown on the upper aspect of the valves, principally of the mitral. The red coloration of the endocardium is a phenomenon of cadaveric imbibition. The mammillated projections are the product of fibrous transformation of little hæmatomata developed on the valves during early life, and perhaps even during intra-uterine life. The histological lesions affect all the elements of the structure of the cardiac muscle; they are met with in the walls of the left ventricle near the apex, and near the columns of the mitral valve. When you dissociate the muscular fibres, you observe that they are very fragile; they are fusiform, tumefied, in many points granular, have large nuclei which stain easily and possess one or more very refractive nucleoli. The muscular fibres may undergo two kinds of degeneration, and present either the granular or granulo-fatty aspect or the vitreous transformation. In the granular degeneration the granulations are irregularly disseminated, or disposed side by side in chaplets along the fibre. In the vitreous degeneration the fibres present one, rarely two or three, degenerated patches in their course. The vitreous block is spherical or fusiform, and crowds to one side the striated substance, swell-

ing the fibre and forming a node in its course. These two modes of degeneration may be met in the same specimen; the fibre interrupted by waxy blocks presents here and there throughout its whole extent a crop of dark granulations. The connective tissue takes on an abnormal development. The internal perimysium is infiltrated with embryonic cells, in the midst of which appear débris of granular muscular fibres, degenerated, or masses of fatty granulations, the last vestiges of atrophied muscular fibres, or, perhaps, little hæmorrhagic foci which testify to vascular intra-muscular ruptures. In short, the diphtheria poison determines both a parenchymatous and an interstitial lesion. It also causes an arterio-sclerosis of the vessels of the heart. The vasa-vasorum situated in the outer coats are the seat of an obliterating endovascularitis. The walls of the arterioles thicken, and their lumen is often filled by a thrombus adherent to their walls.

The blood presents modifications of color and consistence, which are especially seen in the malignant and asphyxiating forms of diphtheria. It is then blackish or brown, and has a sepia tint; more rarely it has the appearance of currant jelly or simply reddish water. It is probable that the fibrin of the blood increases as in most general infectious diseases. The researches of Quinquaud, Lécorché and Talamon and Binaut, have shown that in diphtheria there is an augmentation of the white globules, the more marked

the graver the diphtheria. The number of red globules diminishes, and, according to Quinquaud, the power of absorption of hæmoglobulin for oxygen diminishes as the disease becomes more grave. There is also a great augmentation of the extractive matters of the blood, while the salts of potassa are notably diminished.

The symptoms which seem to depend on the alteration of the nervous system are not always explained by the lesions found at the autopsy. Very complete and extensive paralyses have been noted in subjects whose nervous systems presented insignificant alterations or none at all. We may, then, affirm, in reference to such cases, that the diphtheria poison may profoundly modify the function before altering the organ. The lesions of the peripheral nerves and nerve-roots have been noted in many isolated cases since Charcot and Vulpian, in 1862, noticed in a case of diphtheritic paralysis of the velum pendulum a lesion of the palatine nerves characterized by the reduction to granulo-fatty droplets of a certain number of nerve-tubes, a lesion similar to what is observed at the peripheral end of a divided nerve. Dejerine has studied several cases of diphtheritic paralysis, and has always noticed in the anterior spinal roots a lesion which corresponded exactly by its seat with the paralytic phenomena observed during life, and which was the more marked the longer the paralysis had lasted. This lesion was identical with the Wallerian degener-

ation, characterized by the moniliform aspect of the nerve-tubes, in which the myeline breaks up into fat drops by the complete disappearance of the axis-cylinder and a multiplication of the nuclei of the sheath of Schwann. The posterior roots were normal. The examination of the peripheral nerve was made in only one of these cases. Déjerine noticed these empty nerve-sheaths, in the midst of other tubes that were perfectly normal. He describes, at the same time, slightly marked lesions of the spinal cord, limited to the gray substance, but more particularly to the anterior cornua (nerve-cells less numerous, less refractive; multiplication of the elements of the neuroglia; congestion of the vessels).

Gombault, whose researches have been confirmed by the observations of Gaucher and Meyer, has established the nature of the lesions of the roots and peripheral nerves in diphtheritic paralysis. It is a periaxile segmentary neuritis, of which the Wallerian degeneration is the possible if not necessary termination. There is first a segmentary alteration affecting only a limited extent of the length of the fibre, located in one or more annular segments, often in a part of the segment only. When you follow the same fibre along its entire course you will not fail to meet the same lesion several times, each diseased segment being separated from those nearest by intervals of fibre absolutely healthy. The diseased fibres have a tendency to group themselves into bundles; at the

same time, diseased fibres may be met with in the midst of healthy fibres. The segmentary lesions begin at one of the extremities of the segment; they then gain the other, and finally the middle portion. The lesion takes on two different aspects: there is a phase of degeneration, and a stage of regeneration. These two aspects are frequently associated in the same interannular segment. In the stage of degeneration the myeline becomes granular; in certain points of the nerve tubes there are large protoplasmic masses containing numerous nuclei; elsewhere the axis-cylinder, under the form of a simple tractus, is covered at the level of the granular swellings with myeline, but remains always continuous. When the fibre is regenerated it is thinner at the point where it has been diseased—and the segments that have been affected are shorter than normally—but its sheath of myeline is perfectly homogeneous and is depressed at the level of the nuclei; its contours are sharply arrested. The degeneration of the fibre does not always retrocede, and the axis-cylinder may become interrupted by a sort of spontaneous destruction similar to what we see in acute myelitis. You will note then, in a segment of neuritis, moniliform swellings of the axis-cylinder, which finally fill the primitive sheath; in following the nerve you arrive at a solution of continuity beyond which you no longer find it except under the form of isolated trunks between the blocks of myeline. From this point, where there is

rupture of the axis-cylinder, the entire peripheral end of the nerve fibre undergoes a Wallerian degeneration. Thus you will note these lesions alongside of those of segmentary peri-axile neuritis, of which they are the consequences. Pitres and Vaillard, in examining the nerves in a case of diphtheritic paralysis, have found the lesions described by Gombault. But in the fibres affected with segmentary neuritis they have not been able to stain the axis-cylinders. Lastly, Babinsky has not succeeded in finding the histological lesions of the nerves in experimental diphtheritic paralysis.

The spinal cord has generally presented an aspect nearly normal; in some cases the large motor cells of the anterior cornua were filled with dark, voluminous granulations which completely concealed their nuclei and resembled those met with in the course of myelitis.

The meninges present exceptionally the appearances of inflammation with fibrinous exudation. This meningitis may invade the gray substance of the cord and constitute a meningo-myelitis, involve the whole extent of the bulbo-spinal meninges, or localize itself in the bulb and cervical cord.

In the cerebrum, lesions have been very rarely found; those which have been noted were sanguineous extravasations with peripheral softening, simple cerebral congestion, turgesence of the sinuses, serous suffusion of the meninges, œdema of the ventricles, etc.

Inflammation of the meninges is quite exceptional and is always due to secondary infections.

The muscles may be altered in diphtheria; writers have noted granular degeneration of their fibres. The fibrillary elements of the primitive fasciculi lose their cohesion and easily separate; their transverse striation is effaced; the fibres contain proteinaceous or fatty granulations, but there is no alteration of neuclei or sarcolemma. Labadie-Lagrave has reported a case in which the muscles presented the waxy transformation. These alterations have been especially studied in the muscles subjacent to the inflamed mucous membranes, larynx, and soft palate. They are pale, of a dead-leaf color, œdematous, and friable. In the larynx the extrinsic muscles are rarely degenerated; it is the thyro-arytenoidei which are most generally affected.

3. Lesions Due to Secondary Affections.— Ulceration and gangrene of the mucous membranes are exceptional in diphtheria. We have seen, however, that the diphtheritic poison may of itself in certain cases determine losses of substance in mucosæ covered with false membrane. The streptococcus *pyogenes*, so often associated with the Loeffler bacillus, may also penetrate the mucous membranes and determine profound ulcerations: the case is similar to that observed in the pseudo-diphtheritic anginas of scarlatina where we find extensive losses of substance underneath the false membrane, and can easily stain by Gram's method

the micrococci in chains which profoundly penetrate the diseased mucosa. When the subject is very much debilitated, and the microbes of putrefaction obtain a habitat in these ulcerations, the base becomes tomentous and grayish, the borders are excavated, and there is gangrene at the level of the losses of substance. This is met with on the tonsils and soft palate, where it may cause perforation. The gangrene may penetrate the cellular tissue below the mucosa and extend to the large vessels of the neck. Necrosis of the larynx and its cartilages is rare. The gangrene may be complicated with cutaneous diphtheria and invade the tracheotomy wound after this operation.

The histological lesions of the glands have been well studied by Œrtel and Morel. These alterations pertain especially to the follicles, which stain poorly by picro-carmine. Little alveolar abscesses form in the necrosed connective-tissue stroma. In points where the lesion is less advanced, we see in the region of the follicles a finely granular amorphous tissue in which may still be seen a few round-cell elements, which stain indifferently by carmine and present the characters of coagulation necrosis. Masses of streptococci are found in the little alveolar abscesses and degenerated follicles.

The inflammations of the endocardium or meninges are complications quite exceptional in diphtheria.

The cutaneous modifications corresponding to

erythemata have been studied by Lewin and Leloir. They present nothing that is special to diphtheritic erythemata. We know that each arteriole of the skin irrigates a little circular territory, the arteriole dividing and spreading itself out into ramifications in the form of a cone, of which the base is tegumentary. If an arteriole is paralyzed, all the corresponding territory is congested and forms a red spot. At the onset of an erythema, the congestion usually shows itself in an unequal degree in these different vascular territories, so that paler areas are observed between the red spots before the erythema becomes general. When the blood-pressure equalizes itself over all the vascular territories, the coloration of the skin becomes the same everywhere and we have the scarlatinoid erythema; and if there is exudation under the epidermis, there will be found vesicles or bullæ. When the congestion remains limited to little islets, but is still active and there is œdema and diapedesis from the hyperæmic zones, the eruption takes on the papulo-tuberculous aspect. If the blood-pressure becomes too strong in the territories invaded by the erythema, the red blood-corpuscles issue from the vessels, and we have the purpuric erythema.

The most frequent pulmonary lesion of diphtheria is broncho-pneumonia. It is the consequence of a secondary infection, due to the streptococcus *pyogenes*. This micro-organism is the agent of most of the broncho-pneumonias, whether primary or secondary.

In six cases out of seven the broncho-pneumonia of diphtheria takes on the form of disseminated nodules; the pseudo-lobar form which is met with in one out of seven cases occupies chiefly the posterior bronchial system, generally towards the inferior border.

Atelectasis is constant and always very extensive. It may be the only pulmonary lesion. In no disease but whooping-cough is the vesicular emphysema more marked; rarely it becomes interlobular and subpleural. The abundance of the fibrinous exudate in the alveoli is a character of the broncho-pneumonia of the diphtheritic. In certain cases the fibrin, under the form of ramified and anastomosing tracts, almost fills of itself a whole group of alveoli. This network contains a few leucocytes, red globules, and epithelial cells. Its aspect might lead one to believe that he had before him a frank pneumonia at the period of hepatization, if these points were not immediately surrounded by zones showing wide disparities in the state of development of the characteristic lesion. These abundant deposits of fibrin are met with in cases where the false membranes have extended to the small bronchi, but they are also found in cases where the membranes are arrested at the larynx or trachea; there is, then, no necessary relation between the two processes.

Another elementary lesion whose frequency is rather peculiar to diphtheria, is constituted by hæmorrhagic foci in the midst of the pulmonary parenchyma.

Balzer has made a study of them, and assigns as their habitual seat the posterior and inferior part of the lungs. , The blood effused circumscribes the peri-bronchial nodules, and deforms but never entirely penetrates them. It is probable that we have to do here with hæmorrhages due to the peri-nodular congestion and penetrating the lobules primarily affected with the pneumonia. Microscopic preparations made from sections of the bronchial nodules show the streptococcus, and sometimes the pneumococcus and Lœffler bacillus.

I cannot close this chapter without saying a few words concerning the lesions produced in the organism of animals by experimental diphtheria.

The researches of Babès have shown that the lesions obtained by inoculating the Loeffler bacillus in animals are very like those met with in the organs of children that have died of diphtheria. The similarity becomes much less evident when the inoculation is performed with diphtheritic cultures that have been filtered through porcelain. New researches will be necessary to explain these differences.

TREATMENT.

It is not my intention to review here the innumerable kinds of treatment which have been proposed for diphtheria. Their very multiplicity sufficiently indicates the little efficacy they possess. I shall only attempt to set forth what appear to be the most rational precautions and therapeutic measures for the physician to adopt when he finds himself in the presence of a case of diphtheria. I shall start from the postulate, absolutely demonstrated to-day, that the germ of diphtheria is exclusively contained in the false membranes and products of expectoration, which when dried keep the germ active a long time and may thus easily transmit it in a state of virulency.

When the physician is called to a patient affected with diphtheria, what should he do?

Even when there is some doubt as to the diphtheritic nature of the affection, the same precautions should be taken as if the diagnosis were certain. The carriage which the patient occupies in transit to the hospital must be disinfected immediately after. In Paris we have special carriages placed at the disposal of physicians for such purposes. If the patient is not to be removed anywhere, he must as far as possible be isolated, no one but his regular attendants being allowed access to him. If children live in the house, they should not only be excluded from the room, but if possible sent away during the time

of sickness and till after thorough disinfection of the house has been effected. These same children should also be kept under observation and away from other children during the first fortnight. Nurses and attendants on the patients should rigorously observe the following rules: Take no drink or nourishment in the sick-room; keep the hands clean with a brush and soap-suds, and occasionally rinse them in an antiseptic solution; bathe after every contact with an infected object; renew these ablutions always on leaving the sick-room and before eating. It would be a good plan for every attendant to wear a special suit while in the patient's room; this can be laid aside when he leaves the room. All cracks or abrasions about the hands or face must be instantly painted with collodion. The nurse should avoid taking the patient's breath, especially during fits of coughing. Nor should the nurse neglect to take a walk in the open air once or twice a day, or overlook the necessity of sleeping in a room apart from the patient. Similar precautions are equally necessary for the attending physician.

There are two sorts of antiseptic solutions to be used: one strong, the other weak. The former consists of corrosive sublimate, one part to a thousand; this should be stained with fuchsin, and acidified with ten parts of hydrochloric acid:

Corrosive sublimate, 1 part.
Hydrochloric acid, 10 parts.
Water, 1000 parts.

Useful antiseptic solutions are also the following: cup. sulph., 5-per-cent.; calcium chloride, 5-per-cent.; milk of lime, 20-per-cent.; zinc chloride, 1-per-cent. To obtain a very active milk of lime, take a certain quantity of quick-lime of good quality, and slack it by wetting it slowly with half its weight of water; when the slacking is completed, put the powder in a bottle, cork tightly and set away in a dry place. As a kilogramme which has absorbed 500 grammes of water in order to undergo slacking has acquired a volume of 2 liters 200 cubic centimeters, it suffices to suspend it in double its volume of water (*i.e.*, 4 liters, 400 Cc.) in order to have a milk of lime which shall be about 20 per 100.

The feeble solutions which are most efficacious are the following: corrosive sublimate, 1 per 2000; phenic acid, 5 per 1000; sulphate of copper, 2 per 100; chloride of lime, 2 per 100; milk of lime, 7 per 100. The first two of these feeble solutions are best for the ablutions of the patient or his attendants.

As soon as a case of diphtheria is recognized, all curtains, carpets, wearing apparel, and every article of furniture which is not indispensable should be removed from the sick-chamber, and immediately disinfected, either in the dry stove under steam pressure, or by washings with a suitable solution from among those above mentioned, or by sulphur fumigations. The bed should be located in the middle of the room. Aëration of the room must be effected several times a

day; sawdust wet with one of the strong disinfectant solutions should be sprinkled over the floor every day, the room then swept, and the sweepings immediately burned. The body-linen, towels, bed-clothing, dressings, etc., ought to be immersed for two hours in one of the strong solutions, and then kept in boiling water for half an hour, before the final washing. All objects that have been in contact with the patient may transmit the disease; care must therefore be taken that all surgical instruments, as well as domestic utensils, knives, forks, spoons, cups, etc., after being used, be placed in boiling water, and kept there for five minutes at least. It will be well to destroy all books and playthings which have been handled by the patient.

The matters vomited or expectorated by the patient, the stools, and the urine, should be immediately disinfected with one of the strong solutions. A cupful of the solution having been poured into the vessel, the vomitus, expectoration or dejecta should, immediately after passage, be buried or poured into water-closets which are disinfected twice a day with a strong solution of milk of lime. The better way would be to bury them in a deep hole in the ground, first covering with the strong chloride of zinc or other disinfectant solution. A place should be chosen which is at a distance from any water-source. The dejecta must not be thrown onto manure heaps or into water-courses.

It is important in the presence of a case of

diphtheria that the physician should make a careful inquiry to determine its origin; he will thus often be able to circumscribe and arrest an epidemic. Moreover, every case of diphtheria should be at once reported to the board of health.

All these precautions should be indicated by the physician at the date of his first visit.

Local Treatment.—The prevalent conception of diphtheria, which makes of it a disease quite local at the outset, the patient subsequently being constitutionally poisoned by the products elaborated at the point of infection, gives a capital importance to the local treatment of the disease. Cauterization of the parts invaded by the false membrane is not a new method, and we know the use which Bretonneau and Trousseau made of hydrochloric acid for this end. But the recent conquests of bacteriology have given more assurance to the physician, and he has thereby learned the crucial point to which his efforts should be directed. M. Gaucher was the first to popularize a rational treatment of diphtheria. This method is to-day everywhere employed in this country, though with some modifications. His mode of treatment includes three stages: (1) Ablation of the false membranes; (2) Painting of the diseased parts with a strong antiseptic mixture; (3) Irrigations of the bucco-pharyngeal cavity with a weak antiseptic solution. These three stages of treatment should be

regularly repeated every three or four hours, even during the night, and oftener still if the false membranes are rapidly reproduced.

The ablation of the false membrane is made by means of a soft-wool brush invented by Dr. Crésantignes. The mouth must be opened with a tongue-depressor, and kept open if necessary by means of a wedge, and the false membrane removed very gently, care being taken not to corrode the mucosa and make it bleed. As far as possible the throat should be cleared of all the false membranes which cover it, then painted by means of a suitable swab with the following mixture:

Camphor, 20 Gm.
Castor oil, 15 Gm.
Alcohol, 10 Gm.
Crystallized phenic acid, 5 Gm.
Tartaric acid, 1 Gm.

This mixture is sufficiently caustic to require care on the part of the physician not to touch with it the tongue or the sound parts of the mucous membrane of the mouth.

As fast as the false membranes are detached, and while there remain any floating shreds in the throat, it is well to make from time to time large irrigations of the bucco-pharyngeal cavity and nasal fossæ with a feeble antiseptic solution (phenic acid, 1 per 200). These irrigations are made by means of an ordinary fountain-syringe with straight cannula, care being

taken to have the head of the child bent over a pail or other vessel to prevent swallowing the solution. After each cauterization with the mixture, a period of ten minutes is allowed to elapse, to give the topical remedy time to act, then a copious irrigation is made with a weak solution; in very young children it is better to employ boiled water.

Instead of the Gaucher mixture, the sulphoricinated phenol may be employed with equally good results; the bichloride or biniodide of mercury, 1 part to 200 or 300; or the camphorated phenol.

Crystallized phenic acid, 5 Gm.
Camphor, 20 Gm.
Alcohol, 10 Gm.
Gycerin, 25 Gm.

The camphorated naphthol is a good preparation:

Naphthol, 10 Gm.
Camphor, 20 Gm.
Glycerin, 30 Gm.

Salicylic acid may also be used in weak solution, 1 or 2 per 100.

Perchloride of iron, pure, or mixed with equal parts of glycerin, is also in use; also tincture of iodine; lastly, permanganate of potash, 1:10, with which I have obtained in a series of clinical trials results very similar to those which others claim to have derived from Gaucher's mixture. M. D'Espine prescribes lemon-juice, which is a very old remedy in diphtheria.

Good authorities employ also for irrigations

boric-acid solutions, 3 or 4 per 100; lime-water; chloral-water, 1 per 200; salicylic acid, 1 per 1000; and peroxide of hydrogen.

Some conjoin with the above, antiseptic sprays. With a suitable hand-ball spray-producer, spray the mouth and throat of the patient with the antiseptic solution. Or steam pulverizations with a boric solution may be made, a Codman & Shurtleff atomizer being employed; the steam is directed as far as possible into the mouth of the patient. The atmosphere of the room may also be saturated with antiseptic vapor by keeping constantly evaporating a weak carbolic solution contained in a great open dish. Sevestre advises to place every ten minutes a little piece of ice in the mouth of the patient.

The method of Gaucher, which gives in general very satisfactory results, is not applicable to all cases. The degree of adhesion of the false membrane is very variable. There are diphtherias where the exudate seems to be identical with the mucous membrane, and where all attempt at ablation ends in tearing the mucosa and making it bleed. Often the pseudo-membrane which is easily removable at the onset of the disease, becomes subsequently extraordinarily adherent to the underlying mucosa. Sometimes we encounter infants so refractory that at each swabbing we run the risk of making a traumatism more or less deep in the mouth or in the throat with the tongue-depressor or with the swab forceps, especially when

the attendant does not well succeed in keeping the child still. It seems to me that these are real contra-indications against swabbing. Such is, moreover, the opinion of M. Roux, who said recently: "I am not at all an advocate of forcible swabbing and ablation of the pharyngeal false-membranes. By these methods one cannot help continually wounding the surface of the tonsils. In destroying the false membranes you destroy also certain parts of the mucosa, and you create new points of absorption for the toxine which is being continually produced by the microbes which pullulate in the epithelium. It will not do to believe, in fact, that even when you have removed all the white patches in the throat you have removed all the cause of the evil; it is far otherwise. There remains always a residuum of bacilli that the most energetic brushings cannot remove. In my judgment it is better practice to content ourselves with antiseptic irrigations, abundant and repeated, made with care and gentleness." The practitioner will, then, limit himself to irrigations of the throat with one of the solutions which I have indicated above, whenever he has reason to fear that, by attempting to swab, he will wound the mucosa.

The local treatment which I have described is chiefly applicable to diphtheritic angina; but it is also employed, whatever may be the seat of the false membranes, whenever they are directly accessible.

When the diphtheria is developed on a cutaneous

surface, it is necessary besides to cover the wound with an occlusive dressing which will prevent the dissemination of the disease.

Whenever the false membrane invades the larynx it constitutes a mechanical obstacle to respiration which may necessitate tracheotomy. I shall not here describe this operation or its sequelæ; but it is well to remember that, except in certain cases where the very intense and oft-repeated paroxysms of suffocation threaten sudden death, it is the rule not to operate until the period of asphyxia, when to the extinction of the voice and the cough is added a dyspnœa not only paroxysmal but permanent, with wheezing and signs of blood-stasis in the capillaries. It is better, in short, to operate at the latest possible moment, and not to forget that often an emetic suitably administered has enabled the physician to avoid an operation which before seemed necessary.

General Treatment.—At the same time that we combat the infection we must arm the organism against the intoxication by subjecting it to an appropriate general treatment, of which alimentation and tonics form the basis.

It is needful, above all, to nourish the patient as fully as possible. It is also necessary to overcome the dysphagia, and the repugnance which the patients rapidly manifest toward food; to have recourse to semi-solid and very substantial articles of diet in

small volume, such as eggs, meat-juice mixed with thick gruel, creams, scraped or very finely hashed meat. The physician will employ, in case of necessity, gavage (forced feeding) and even nutritive enemata. Alcoholic stimulants give also good results, on condition that they are diluted with water and given in small quantities at a time. According to the taste of the patient, he may be allowed to take freely sherry, Malaga, champagne or Bordeaux wine, whiskey punch, tea and coffee. All these liquids are better tolerated and more easily swallowed when they are cold, and even ice-cold.

I am in the habit of giving cinchona, under the form of the soft extract, in the dose of two to four grammes per day, in infusion of coffee:

℞ Inf. coffee, 125 Gm.
Syr. acaciæ, 40 Gm.
Soft ext. cinchona, 2 to 4 Gm.

M. S.: Tablespoonful every two hours.

Some think highly of hydrochloric lemonade, 4 per 1000—taken continually by spoonfuls during the day; perchloride of iron, in the dose of one to two drops (liq. ferri chloridi) every two hours; eucalyptol, dissolved in liquid vaselin, in subcutaneous injection; two to five grammes of benzoate of soda per day in a potion; hypodermic injections of caffeine or of ether; lastly, inhalations of oxygen.

Treatment of Certain Signs of Intoxication.—When the glandular engorgement takes on considerable proportions, the practitioner may make inunctions of mercurial ointment over the swollen parts, or he may keep on cold applications, and even apply an ice-bag.

In general, the albuminuria is too transitory to indicate a lasting lesion of the kidney. If, however, it is persistent and remains abundant, it will be desirable to put the patient on a milk diet, while continuing to stimulate him with a little brandy.

In cases where the gastro-intestinal symptoms assume a certain importance, it may be well to practice intestinal antisepsis by betol or benzo-naphthol.

Hæmorrhages are rarely so abundant as to require treatment; they imply a profound alteration of the economy which calls for tonics and stimulants.

When the heart is gravely affected by the diphtheritic poison, and even when it begins simply to be enfeebled, it will not do to hesitate to resort to the cardiac tonics. Caffeine gives the best results, administered in potion or in hypodermic injection. In the adult one to two grammes of caffeine may be given per day; in the infant, 25 to 50 centigrammes. Black coffee may be taken at the same time. When myocarditis is made manifest by incontestable signs, give ergotin in the dose of two to four grammes in twenty-four hours. Cutaneous revulsion over the præcordial region seems to present more disadvan-

tages than benefits. Diuretics and the milk diet are indicated in order to cause the elimination of as much as possible of the poison by the renal emunctory.

For the diphtheritic paralysis the physician can do little but feed the patient and electricize the enfeebled muscles. Alimentation should be very carefully watched. It is necessary to diminish as much as possible the quantity of liquid aliments when the soft palate is affected by the paralysis. Fluids are then rejected by the nares, or flow into the respiratory passages, provoking violent paroxysms of coughing, which fatigue the patient and cause repugnance toward food. Likewise solid food constitutes a danger always threatening; fragments insufficiently masticated may fall into the trachea and determine an access of fatal suffocation. It is better to give panada, thick soups, stews, pap. It may become necessary to employ the œsophageal sound to introduce aliments. At the same time, it is necessary to have recourse every day to faradization of the paralyzed muscles. Some have counseled the galvanic current, for which success has been claimed; the negative pole is placed on the back of the neck, the positive pole over the paralyzed parts.

When the paralysis begins to amend, we may attempt to excite the muscular contractility by giving preparations of nux vomica. It must be remembered, however, that at the onset of the paralysis this is in-

jurious rather than useful. The various tonics, hydrotherapy, sulphur baths and sea baths are still precious adjuvants.

Treatment of the Secondary Infections.— When below the false membranes there appear patches of sphacelus of considerable extent, it will not do to neglect repeated antiseptic irrigations, and particularly the employment of dioxide of hydrogen; the attempt must especially be made to modify the soil by building up the organism through super-alimentation and tonics.

The suppurative adenites should be incised early, especially if the pus has invaded the cellular tissue adjoining the inflamed glands. The least delay at this time may permit burrowing of the pus into the deep regions of the neck, or even to the mediastinum. It must also be remembered that often these abscesses comprise two pockets, united by a narrow tract; the abscesses should be opened by a free incision, including both cavities.

It is necessary to cover with occlusive and antiseptic dressings all suppurative lesions of the skin or cellular tissue (impetigo, whitlows, etc.) which are susceptible of being infected by the diphtheritic bacillus.

Treatment may be efficacious in the tardy broncho-pneumonias; it is rarely so in the early forms. At the onset, emetics have been recommended; these, however, should not be continued, on account of the

gastric troubles which they entail. The physician should have recourse to generous diet (milk, broth, in small quantities), tonics, and alcohol. Legroux employs systematically as internal treatment, glycerinized creosote in rum, to combat and even to prevent the broncho-pneumonia. Potions may be given containing an expectorant (kermes, or the white oxide of antimony) or tincture of digitalis. Dry cups constitute an excellent means of revulsion, preferable to the fly-blister. The latter should be absolutely proscribed in young children, mustard sinapisms being used instead. Following tracheotomy, certain prophylactic measures against broncho-pneumonia are absolutely indispensable: a muslin band passed across the orifice of the cannula, a constant temperature from 16° to 18° C. (57° to 61° F.), and saturation of the atmosphere of the room with the vapor of carbolic acid from a plate containing this liquid in a state of evaporation.

Hygiene of Convalescence.—We know that frequently, when the false membrane has disappeared, the diphtheria bacillus still maintains a habitat in the mouth of the patient, and with all its virulence. It is necessary, then, long to continue the antiseptic lavages of the buccal cavity. It is also well to keep the convalescent away from other children for a month or more. Before allowing him to associate with other children again, it will be pru-

dent to make him take one or more sublimate baths, or, if that be not possible, a bath of soap and water, followed by lotions of corrosive sublimate 1:1000. At the end of convalescence, to complete the toning up of the constitution, the patient may be sent away for change of air, to the country or sea-side.

All the objects which have served for the daily use of the patients must be disinfected at this time if they have not been before. This disinfection is effected by prolonged boiling, or by exposure to steam under pressure.

The room that the patient has occupied must not be again used until after complete disinfection by one of the following processes:

1. *Disinfection by Corrosive Sublimate.* Disinfection of the bare walls and ceilings should be made methodically by means of sprayings with the strong solutions of corrosive sublimate. The sprayings should be begun at the upper part of the walls, being made along a horizontal line and successively carried downwards, so that the entire surface of the walls shall be covered with a fine stratum of the pulverized liquid. The ceiling should be sprayed in the same manner. The floors, wainscoting and mantels should be washed with boiling water and wiped, then flooded with the sublimate solution; and the room should not be occupied again until after being thoroughly ventilated for at least twenty-four hours.

In case the sick-room has been covered with wall-

papers it will be well to have these scraped off before the disinfection, even at the expense of repapering the room.

2. *Disinfection by Sulphurous Acid.* Paste a few strips of paper over all cracks which may allow the sulphurous vapors to escape. Remove wall papers and scrape the walls. Burn sulphur, thirty to forty grammes per cubic meter, in the room. To prevent the danger of fire, place the vessels containing the sulphur in the centre of iron basins containing a little water. In order to ignite the sulphur, wet it with a little alcohol. Before fumigating the room, it is well to saturate the atmosphere with the vapor of boiling water, for it has been demonstrated that the antiseptic action of sulphurous acid is increased when it is mixed with the vapor of water. When the sulphur is ignited, close the doors and windows. The room must be kept closed for twenty-four hours; then the doors and windows are opened wide, and left open for forty-eight hours that the sunlight and air may have free access.

When a region is the seat of an epidemic of diphtheria, it is well, whenever this is possible, to remove far from the centre of contagion all persons susceptible of contracting the disease, particularly children. Careful supervision should be made of the drinking-water, which should be of perfect purity, and it is better always to use boiled water for cooking and for drinking.

The washing of contaminated clothing in water-courses should be prohibited, and such streams should be especially kept free from the dejecta of patients.

Milk may serve as a vehicle for the diphtheritic contagion, and should always in times of danger be boiled before being used.

We have seen that there exist in domestic animals certain pseudo-membranous affections which do not appear to have the same origin as human diphtheria. When these diseases have been observed in a stable or barnyard it will be well to isolate the affected animals, more for the safety of the animals remaining healthy than to arrest an outbreak of human diphtheria.

There are certain general measures of public hygiene which should be attended to. All the causes which prepare the soil for the invasion of epidemics should be removed when diphtheria prevails. It is necessary to have a close supervision over groups of children such as are assembled in schools, and in times of epidemic make frequent examinations of the throat; and school children should be required twice a day to gargle the mouth with an antiseptic solution. Should several cases of diphtheria occur at short intervals in a school, there should be no hesitation in closing the school. Besides, the rules of general hygiene applicable at all times should be still more rigorously observed, especially in what concerns the purity of the drinking-water; aggregations of indi-

viduals, as on holidays and at fairs; the superintendence and provisioning of the markets; the cleanliness of the soil; the careful control of water-sources, and the investigation of possible causes of infection; the regular removal of all night-soil; the cleanliness of dwelling-houses; the careful inspection of work-shops, dock-yards, etc., destined for the laboring and industrial population; the purification and regular disinfection of water-closets, public and private; and the maintenance of a perfectly intact and well flushed sewerage system.

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